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(54) Title: STANDING WAVE DESIGN OF SINGLE AND TANDEM SIMULATED MOVING BEDS FOR RESOLVING MULTICOMPONENT MIXTURES

(57) Abstract: Separations of one or more components from multi-component fluid mixtures using simulated moving bed technology, and methods of designing such simulated moving beds (SMBs), are provided. The SMBsdesigned according to this invention can be used to separate slow and fast moving fractions in multicomponent mixtures, or to separate an intermediate affinity component from the mixture. The invention is applicable to systems exhibiting linear isotherms, and is especially applicable to such systems when separations are inhibited by mass transfer resistances.

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STANDING WAVE DESIGN OF SINGLE AND TANDEM SIMULATED MOVING BEDS FOR RESOLVING MULTICOMPONENT MIXTURES

REFERENCE TO PRIOR APPLICATIONS

This application claims priority to United States Provisional Patent Application Number 60/204,700, filed May 16, 2000, and U. S. Provisional Patent Application Number 60/204,701, also filed on May 16, 2000.

FIELD OF THE INVENTION

This invention relates to separations of one or more components from multi-component fluid mixtures using simulated moving bed technology, and to methods of designing such simulated moving beds (SMBs). The SMBs designed according to this invention can be used to separate slow and fast moving fractions in multicomponent mixtures, or to separate an intermediate affinity component from the mixture. The invention is applicable to systems exhibiting linear isotherms, and is especially applicable to such systems when separations are inhibited by mass transfer resistances.

BACKGROUND OF THE INVENTION

Principles of Simulated Moving Bed Chromatography

Liquid chromatography is widely used in industry for separating and purifying components in liquid and gaseous mixtures. However, most applications of liquid chromatography are batch chromatographic processes, which give low yields, consume high quantities of eluent, utilize adsorbent inefficiently, and are labor intensive. Moreover, the discontinuous nature of batch chromatography, and the dilution of collected components, limits its attractiveness for pilot-plant and process-scale separations.

To improve the efficiency of chromatographic processes, continuous moving beds ("CMBs") consisting of a column that supports counter-current contact of mobile and solid (adsorbent) phases have been proposed (Berg, 1946; Kehde et al., 1948; Ruthven and Ching, 1989). The solid phase, which moves in a downward direction driven by gravity, exits the column at the bottom and is recycled to the top. The mobile phase enters the column at the bottom, is pumped upward, and exits at the top from which point it is recycled to the bottom of the column. This system has two liquid inlets (a feed inlet and a desorbent inlet) and two liquid outlets (a raffinate outlet and an extract outlet).

The feed (containing 2 or more components to be separated) is injected continuously into the middle of the column. As long as the affinity of the components for the solid packing is different, one can choose mobile phase and adsorbent flow rates for the column that will cause one component to move in an upward direction and another component to move downward leading to a spatial separation. This system has two outlet lines: one located beneath the feed where the slower moving component is continuously removed (the *extract*), and one located above the feed where the faster moving component is removed (the *raffinate*). Desorbent is added to the system at the bottom to help push the slower component back up into the column (and to make up for desorbent withdrawn through the extract and raffinate streams).

Continuous moving bed systems offer a number of potential advantages over batch chromatography, including:

- The systems can produce products of purity similar to or higher than batch chromatography, at yields substantially greater than batch chromatography.
- The systems use less desorbent than batch chromatography.
- The systems use the solid phase much more efficiently than batch chromatography.
- The systems require much less column volume (often by an order of magnitude) than batch chromatogram systems, for the same throughput.

These advantages have not been realized in true CMBs, however, because of difficulties inherent to operating and maintaining a CMB unit. The continuous physical movement of solids leads to particle attrition, and considerable difficulty can be experienced maintaining strict plug flow of both solid and mobile phases. These problems greatly reduce process efficiency and useful life of the adsorbent, and impose severe limitations on the mechanical properties of the adsorbent particles.

To overcome the problems associated with solid flow in true CMBs, simulated moving beds have been developed. Simulated moving beds are reviewed generally in Ruthven and Ching (1989). Simulated moving bed (SMB) processes realize the counter-current movement of solid and liquid phases and the concomitant advantages of continuous moving beds over batch chromatography without the physical movement of solids. A typical SMB process has four zones with two inlet ports (feed and desorbent) and two outlet ports (raffinate and extract), as shown in Figure 1. SMB processes utilize a series of adsorbent columns connected to form a circuit. Each zone typically contains two or more

evenly sized columns, and these columns are connected to form a continuous circuit. The solid movement is simulated by periodically moving the inlet and outlet ports one column forward in the direction of flow of the mobile phase, so that the product ports are always near the partially separated concentration waves of products in the system. Similar to the continuous moving bed system, the port switching time, zone length, and zone flow rates are all balanced to attain a desired level of purity of the raffinate or the extract.

The function of each zone in an SMB is as follows: (1) Zone I: This zone is located between the desorbent inlet and extract withdrawal and is used for desorbing the slow fraction. A portion of the stream leaving this zone is withdrawn as the extract while the remainder flows into zone II. (2) Zone II: This zone is used for desorbing the fast fraction. (3) Zone III: This zone is used for adsorbing the slow fraction, and separating the slow fraction from the fast fraction. The fast fraction is partially withdrawn at the raffinate port. (4) Zone IV: This zone is used for adsorbing the fast fraction as well as desorbent recovery. The stream leaving this zone should ideally contain only pure desorbent which is recirculated to the desorbent inlet for reuse.

Reported Applications of Simulated Moving Bed Chromatography

SMB separations were first applied in an industrial plant by Universal Oil Products (UOP) for the purification of hydrocarbons (Broughton and Gerhold, 1961; Broughton, 1968; Broughton et al., 1970). UOP's process eventually evolved into what it now calls its Sorbex process. The principal application for UOP's Sorbex process is in the purification of xylene isomers. Indeed, Parkinson et al. (1994) reports that by 1994, UOP had installed 85 SMB units for use of its Sorbex process, and that most of these had been installed at petroleum refineries for p-xylene purification.

UOP's Sorbex process for the purification of p-xylenes has several unique features. First, it separates p-xylene from a mixture of xylene isomers and other phenyl derivatives from the xylene manufacturing process. The process uses a zeolitic solid adsorbent that selectively adsorbs p-xylene. The process also relies upon a displacing component which competes for adsorbent with p-xylene and the other components in a concentration dependent fashion, to prevent cross-contamination of the raffinate and extract.

Parkinson et al., (1994) also reports widespread use of SMB processes for the separation of sugars. For example, Parkinson *et al.* reports that from 1980 to 1994, U.S. Filter had installed approximately 60 SMB units for the separation of sugars. In 1994, U.S. Filter had piloted SMB systems for the separation of lactic and citric acids, glycerine,

glycols, amino acids, and herbicides. In 1994, UOP reportedly installed HPLC SMB in pharmaceutical plants.

In the same year, Soken (Japan) reportedly finished a one-year pilot test of a continuous HPLC system that can purify three-component mixtures and has six columns. Other applications for SMBs have been reported in the literature (Ching et al., 1993; Pais et al., 1997; Ruthven and Ching, 1989). More recently this technique has been developed for the separation of chiral compounds and the purification of biochemical and pharmaceutical products (Nicoud et al., 1993; Pais et al., 1997; Pedeferri, et al., 1999; Lehoucq et al., 2000). The following discussion summarizes some of the literature references disclosing SMB separations.

Sugars: Several processes have been developed for separating and purifying sugars. For example, using a calcium form cation exchange resin, Balannec et al. (1993) and Barker et al. (1960) report using SMB processes to separate fructose from sucrose, and xylose from arabinose. Balannec et al. (1993) also discloses an SMB process in which dextran is fractionated using a size exclusion process on silica gel.

Desalting: Several SMB processes have also been reported for removing salts from mixtures. For example, Maki (1987) discloses an ion retardation process for separating glucose and sodium chloride; Nicoud (1998) discloses an ion exclusion process, using a sodium form cation-exchange resin, for the separation of glycerol and sodium chloride; and Hashimoto et al. (1988) discloses a size exclusion process for separating proteins from ammonium sulfate.

Protein purification: At least four SMB processes have been developed for the purification of proteins. For example, Huang et al. (1986) discloses the separation of trypsin from a porcine pancreas extract using affinity chromatography; Houwing (1996) reports the fractionation of human serum albumin using a two column system; Nicoud (1996) reports the separation of myoglobin from lysozyme using an adsorption process; and Schulte et al. (2000) reports reversed phase and silica gel adsorption processes for separating cyclosporine A, cyclic oligopeptides, and various impurities.

Ionic Molecules: At least two references disclose the use of SMB processes for separating ionic molecules. For example, Van Walsem et al. (1996) discloses the separation of betaine from molasses using two ion exchange columns; and Maki (1992) reports the separation of L-glutathione from glutamic acid using a cation-exchange resin.

Organic solvents: SMB processes have also been reported for the separation of organic solvents. For example, Szpepy et al. (1975) reports the SMB separation of various C_{16}-C_{22} methyl esters of fatty acids using an undisclosed stationary phase; and Blehaut et al. (1996) discloses the separation of stereoisomers of phytol using silica gel.

Optical isomers: SMB process have found special interest of late in the separation of optical isomers. Fuchs et al. (1992), for example, discloses the separation of threonine isomers using a ligand exchange resin; Balannec et al. (1993) discloses the resolution of racemic 1a-2,7,7a-tetrahydro-3-methoxynaphthyl-(2,3-b) oxirane using microcrystalline cellulose triacetate; and Archibald et al. (1999) reports the separation of epoxide diastereomers using reversed phase, normal phase, or chiral stationary phase SMB chromatography.

Despite these reports, SMB technology still has not made it into the mainstream of industrial separations. Indeed, in an article written as recently as 1995, Hill (1995) stated, "The technique of simulated moving bed chromatography has been around for a considerable time in industry, although for commercial reasons much of the work remains unpublished. Due to problems associated with engineering this technique, its use has been restricted to simple separations where the quality requirements of the product are fairly low."

Overview of Design Strategies

The successful design and operation of a SMB depends upon the correct selection of operating conditions (zone flow rates and switching time), which cause the slow and fast moving components to travel in opposite directions relative to the feed port. In a linear isotherm system, the primary operating conditions are the zone flow rates and port switching time in zones II and III, because these are the two zones where separation initially occurs, and where the zone flow rates and port switching times must be suitably balanced. The port switching time and the flow rates in zones I and IV are also important in order to prevent migration of fast and slow moving components between zones I and IV. However, one can generally compensate for such risk (at the expense of process economics) by increasing the input of desorbent to the system and the rate of raffinate withdrawn from the system.

Several procedures have been proposed in the literature to guide the initial selection of zone flow rates and port switching time. Some of these, based on the approximation of the unit as a series of equilibrium stages and then on the application of a McCabe-Thiele-

like analysis, have been reviewed by Ruthven (1984) and more recently by Hashimoto et al. (1993). An alternative approach is based on the local equilibrium theory, which can be used for linear and nonlinear adsorption isotherms. (Helfferich and Klein, 1970; Rhee et al., 1971; Storti et al., 1989). The local equilibrium theory is generally applicable for ideal systems, i.e., those systems in which mass transfer effects are negligible. See also, Ruthven and Ching (1989); Adachi (1994); Storti et al. (1993); Pais et al. (1997); and Strube et al. (1997).

Figure 2 illustrates the triangle theory (Storti et al., 1989) based on the local equilibrium theory, and how it is employed to arrive at zone flow rates and port switching time in zones II and III. By performing an equilibrium analysis (which assumes no mass transfer effects) one is able to plot a two dimensional triangular region on a graph with dimensionless velocities in zones II and III along the x and y axes respectively. The dimensionless velocities represent net zone flow velocities divided by port movement velocity. The triangular region defines the complete set of operating conditions that will guarantee complete separation (100% purity and yield) of the fast and slow moving components in zones II and III.

The triangle method is useful but it is limited to ideal conditions (i.e. without mass transfer resistances). Therefore, the design does not give any information concerning zone length, mass transfer resistances, or desired product purity and yield. To determine the effects of mass transfer, on zone length and product purity and yield, one must perform a series of computer simulations in which mass transfer resistances and product purity and yield are defined. The results of these simulations can be plotted to define a smaller triangular region, which defines the entire region of relative velocities of mobile phase and port movement in zones II and III which guarantee separation at the defined purity and yield. This is illustrated in Figure 3, wherein each of the smaller triangular regions corresponds to a different set of mass transfer resistances.

Once again, the minimum desorbent consumption for nonideal systems can only be approximated from the triangle theory through a lengthy series of trial and error computer simulations of operating conditions within the triangular region, to determine the desorbent consumption associated with each combination of flow rates in zones II and III, and hopefully to converge eventually on an approximate minimum desorbent consumption. Azevedo and Rodriguez (1999) proved using computer simulations that the standing wave analysis solution (Ma and Wang, 1997) corresponds to the vertex point of the triangular

region. The vertex point gives the highest throughput and the lowest desorbent consumption (see Figure 3).

The aforementioned method is used to estimate the operating conditions for a given SMB system. To have an overview of SMB process design, Figure 4 is drawn to show the parameters that can be varied to explore system efficiencies and the parameters that should be estimated in the design.

In addition to the simulations needed to accommodate mass transfer effects, and the simulations needed to arrive at a minimum desorbent consumption, computer simulations must also be performed each time one of the foregoing parameters (Figure 4) is varied to optimize the efficiency of the system. A designer attempting to scan SMB designs to determine which is most economical, exploring just four values for each of the foregoing parameters, would need to perform 4^{10} (1,048,576) computer simulations (each of which can run for several minutes to hours). As a consequence, designers always make a series of initial assumptions about the SMB that significantly limit the universe of SMB designs that can be explored.

One of the most important variables is the combination of mobile phase and stationary phase. The mobile phase can significantly affect process performance and cost because (1) the mobile phase governs the solubility of solutes in the system, and the maximum throughput on a solid concentration basis, (2) the mobile phase may affect selectivity and effective adsorbent capacity, (3) some mobile phase must continuously be replenished, and (4) some of the mobile phase must be separated from the final product, and separation costs can vary from solvent to solvent. The solid phase, and the size of particles in the solid phase, can similarly have substantial effects upon process performance and cost because (1) the solid phase dictates the absorbent capacity of the system, the selectivity, and the attendant maximum throughput, and (2) the size and type of solid phase dictates the allowable pressure drop and maximum mobile phase velocity.

Another parameter which can significantly influence the efficiency of a particular system, but which is rarely explored through computer simulations, is the total column length (= number of total columns × column length) and zone lengths (= number of columns in each zone × column length) of the SMB. The designer typically assumes: (1) a fixed number of columns, and (2) an allocation of columns among the zones, when initiating the trial and error computer simulation process to determine zone flow rates. However, the

allocation of columns can significantly affect the efficiency of the system, and can even determine whether a desired separation is possible.

Yet another parameter that can significantly affect the efficiency of a particular system, which is unique to multicomponent separations in which a component having an intermediate affinity is desired, is splitting strategy. Such separations typically require tandem or parallel SMBs in which the intermediate affinity fraction is successively separated from the fast and slow moving fractions. When splitting multicomponent mixtures several sequences of splitting can be observed. In a two ring split, for example, one must decide whether to split the intermediate fraction from the fast or slow moving fraction in the first ring. Another option (not mentioned in the prior art) is whether to allow the component that is not being split in the first ring to distribute in the first ring, and thereby contaminate both extract and raffinate streams. Once again, prior art methods would require inordinate numbers of computer simulations or experiments to be performed to evaluate the efficiency of each of these options.

In a recent study by Ma and Wang (1997), a standing wave analysis method for binary separation is developed for continuous moving bed (CMB) and SMB systems with linear isotherms. The analysis is based on the idea that a key concentration wave in each zone can migrate at the same speed as the port movement velocity (or be kept standing with respect to the ports) in order to ensure product purities (Figure 5). By properly selecting the four zone flow rates and solid movement velocity in a SMB, the adsorption wave of the fast fraction can be kept standing in zone IV and its desorption wave can be kept standing in zone II, while the adsorption wave of the slow fraction is kept standing in zone III and its desorption wave is kept standing in zone I (Figure 5). Under the standing wave conditions, Ma and Wang (1997) proposed a set of algebraic equations for binary systems that exhibit linear isotherms and significant mass transfer resistances, to link product purity and yield to zone lengths, zone flow rates, port switching time, and retention and mass-transfer parameters.

The standing wave analysis proposed by Ma and Wang (1997) represented a significant advance in the design of binary SMBs, because it eliminated the need to perform numerous computer simulations or experimental trials when designing SMBs. Computer simulations could still be performed, but typically only to validate the results of the standing wave analysis. However, the standing wave analysis described by Ma and Wang (1997) was limited to binary SMBs, and thus did not show how to design and operate an SMB for

multicomponent separations. Ma and Wang (1997) also did not show how to overcome a number of other issues associated with the design of SMBs, especially SMBs for multicomponent separations, including column allocation issues, splitting strategies, and how to account for fronting and extra-column dead volume effects.

It is an object of the present invention to extend the standing wave concepts of Ma and Wang (1997) to SMB multicomponent separations in which mass transfer effects are observed.

It is another object of the present invention to eliminate, or substantially reduce, the use of computer simulations when estimating the effect of mass transfer in the design of SMBs for multicomponent separations.

Another object of the invention is to provide algebraic equations that eliminate the need to perform computer simulations when optimizing design and operating parameters of SMBs for multicomponent separations, such as desorbent consumption, column allocation and number, and desorbent/adsorbent combination.

It is still another an object of the invention to provide SMBs for separating multicomponent mixtures under linear isotherm conditions wherein non-negligible mass transfer resistances are observed, and desorbent use is minimized for a particular rate of feed.

Another object of the present invention is to provide SMBs for separating multicomponent mixtures under linear isotherm conditions wherein non-negligible mass transfer effects are observed, using column configurations that maximize economic efficiency.

Still another object of the present invention is to provide SMBs for separating multicomponent mixtures under linear isotherm conditions in two or more rings, and methods of designing such SMBs, using splitting rules that optimize economic efficiency.

Yet another object of the invention is to use the design methods of Ma and Wang (1997) in the optimization of design and operating parameters of SMBs for binary separations, such as column allocation and number, and desorbent/adsorbent combination.

Another object of the present invention to provide SMBs for separating binary mixtures under linear isotherm conditions wherein non-negligible mass transfer effects are observed, using column configurations that maximize economic efficiency.

SUMMARY OF INVENTION

The inventors have surprisingly discovered the design parameters for purifying a component or fraction from any multicomponent mixture using SMB chromatography, under conditions that minimize desorbent consumption for a given rate of feed when linear isotherms and non-negligible mass transfer resistances are observed. Unlike prior design methods for multicomponent separations in which the determination of initial operating parameters (i.e. zone flow rates and port movement velocity) were made without considering mass transfer effects, and the operating parameters had to be repeatedly revised through a trial and error process based upon computer modeling that accounted for the mass transfer effects, the present invention accounts for mass transfer effects when the initial operating parameters are derived, using a novel extension of the standing wave analysis previously reported by Ma and Wang (1997) for binary separations.

In particular, the inventors have discovered which concentration waves must stand in which zones to achieve a desired separation, in systems that contain three or more components. (Figure 6). Thus, in one embodiment the invention provides a method of designing an SMB for separating a desired fraction or component from a first fraction or component, in a mixture of N components:

a) providing equations that relate the design, operating, and intrinsic engineering parameters of a SMB that displays linear isotherms, wherein the equations assume standing wave conditions for each of the zones;

b) prescribing a first set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to solve the equations for separating the multicomponent mixture in a first SMB; and

c) solving the equations.

In a preferred embodiment, the SMB comprises a first ring A that comprises four zones, and the equations assume the following standing wave conditions in each zone:

i) in zone I: the desorption wave of component N;

ii) in zone II: the desorption wave of component j;

iii) in zone III: the adsorption wave of component j+1; and

iv) in zone IV: the adsorption wave of component 1; wherein the components are numbered 1 . . . j, j+1, . . . N in order of increasing affinity for the stationary phase, and a split is desired between components j and j+1.

Because the design eliminates the need to repeatedly revise operating parameters in a computer simulation to account for mass transfer resistances or to minimize desorbent consumption, the method enables for the first time SMBs for separating multicomponent mixtures wherein mass transfer resistances are observed and desorbent consumption is minimized. Thus, in another embodiment the invention provides a process for chromatographically separating a desired component or fraction from a multicomponent mixture, under linear isotherm conditions wherein non-negligible mass transfer resistances are observed, comprising:

a) providing a simulated moving bed that comprises a first ring and a first desorbent stream;

b) providing a first feed stream that comprises the desired component or fraction and a first component or fraction,

c) introducing the first desorbent stream and the first feed stream to the first ring under conditions sufficient to separate the desired component or fraction from the first component or fraction, and to minimize the rate of the first desorbent stream; and

d) withdrawing the desired component or fraction as a raffinate or extract from the SMB, separated from the first component or fraction.

The method can be used to design SMBs in which more than one separation is required, and more than one ring is employed. For example, SMBs can be designed to separate an intermediate affinity component from a multicomponent mixture using two or more rings connected in series, in which the slower and faster components or fractions are successively separated from the desired end component. Thus, in another embodiment the process further comprises:

a) introducing a second desorbent stream and the desired component or fraction from the first ring to a second ring, under conditions sufficient to separate the desired component or fraction from a second component or fraction, and to minimize the rate of the second desorbent stream; and

b) withdrawing from the second ring an extract or raffinate that comprises the desired component or fraction separated from the second component or fraction.

The standing wave analysis enables SMBs to be designed and operated for multicomponent systems in which mass transfer resistances are observed, for the first time

without undue trial and error using experiments or computer simulations by: (1) reducing the degrees of freedom associated with the design, and (2) providing a simplified set of relationships that consider mass transfer resistances, desired purity and yield, zone length, and the relationship between feed rate and desorbent consumption, at the initial design stage when determining operating parameters. In a non-ideal linear system, the parameters are represented by the following set of standing wave equations which govern separation in each ring of a single or multi-ring SMB:

$$\nu = \frac{F^{feed}}{SP\varepsilon_b(\delta_{j+1} - \delta_j)} \tag{1}$$

$$\frac{F^{des}}{\varepsilon_b S} = u_0^{I} - u_0^{IV} \tag{2}$$

$$u_0{}^{\mathrm{I}} = (1 + P\delta_N)\nu + \beta_N{}^{\mathrm{I}}\left(\frac{E_{b,N}{}^{\mathrm{I}}}{L^{\mathrm{I}}} + \frac{P\nu^2\delta_N{}^2}{K_{f,N}{}^{\mathrm{I}}L^{\mathrm{I}}}\right) \tag{3}$$

$$u_0{}^{\mathrm{II}} = (1 + P\delta_j)\nu + \beta_j{}^{\mathrm{II}}\left(\frac{E_{b,j}{}^{\mathrm{II}}}{L^{\mathrm{II}}} + \frac{P\nu^2\delta_j{}^2}{K_{f,j}{}^{\mathrm{II}}L^{\mathrm{II}}}\right) \tag{4}$$

$$u_0{}^{\mathrm{III}} = (1 + P\delta_{j+1})\nu - \beta_{j+1}{}^{\mathrm{III}}\left(\frac{E_{b,j+1}{}^{\mathrm{III}}}{L^{\mathrm{III}}} + \frac{P\nu^2\delta_{j+1}{}^2}{K_{f,j+1}{}^{\mathrm{III}}L^{\mathrm{III}}}\right) \tag{5}$$

$$u_0{}^{\mathrm{IV}} = (1 + P\delta_1)\nu - \beta_1{}^{\mathrm{IV}}\left(\frac{E_{b,1}{}^{\mathrm{IV}}}{L^{\mathrm{IV}}} + \frac{P\nu^2\delta_1{}^2}{K_{f,1}{}^{\mathrm{IV}}L^{\mathrm{IV}}}\right) \tag{6}$$

The variables in the foregoing equations are defined as follows:

- N represents the number of components in the system, numbered from low to high affinity as 1, ..., j, j+1, ..., N, and in which a split is desired between component j and j+1
- u_0 is the interstitial velocity
- S is the column cross sectional area
- $\delta_i(\equiv K_{ei}\varepsilon_p + (1 - K_{ei}\varepsilon_p)a_i)$ (a_i is the partition constant between the adsorbed phase and the liquid phase for component i at an infinitesimal concentration, and ε_p is the porosity of the particle)
- K_{ei} is the size exclusion factor for component i

- $P(\equiv \frac{1-\varepsilon_b}{\varepsilon_b})$ is the bed phase ratio
- ε_b is the interstitial bed void fraction
- F^{feed} is the feed flow rate
- F^{des} is the desorbent flow rate
- L is the zone length
- E_b is the axial dispersion coefficient
- K_f is the lumped mass-transfer coefficient
- β is related to the ratio of the highest concentration to the lowest concentration of the standing wave in a specific zone

If product purities (i.e. the purity of the split components in the extract and raffinate), column cross sectional area (S), zone lengths, and feed flow rate are specified, the standing wave equations can be used to find the port movement velocity and the linear velocities of the mobile phase in the four zones of the SMB. These equations define the standing wave conditions when both E_b and K_f are significant. Also, they define the maximum linear velocities for zones III and IV and the minimum linear velocities for zones I and II for a system with linear isotherms. Any lower velocities in zones III and IV and higher velocities in zone I and II result in better than specified product purities and recoveries. However, such designs will have lower throughput or higher desorbent consumption than the standing wave design. The equations also define the minimum desorbent consumption for a given rate of feed, because u_0^{IV} is the highest and u_0^I is the lowest among all the feasible designs that guarantee separation at the prescribed yield and purity.

The standing wave design has greatly simplified the process of maximizing process efficiency, for binary and multicomponent systems, by enabling a designer to scan the various design and operating parameters that can be employed. For example, in systems wherein the selection of desorbent and stationary phase is important to optimize process economics, the equations allow a designer to quickly scan various desorbent/stationary phase combinations, or particle sizes for the stationary phase, to derive operating parameters from which process economics can quickly be assessed. Similarly, using the foregoing equations, one can quickly scan numerous column configuration schemes (varying the total number or length of columns and the allocation of columns among zones) to determine

which is the most efficient for a particular system. Thus, in another embodiment the invention provides a method of optimizing a SMB system that displays linear isotherms comprising:

a) providing equations that relate the design, operating, and intrinsic engineering parameters of an SMB that displays linear isotherms;

b) prescribing a first set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to resolve the equations for separating a binary or multicomponent mixture in a first SMB;

c) prescribing a second set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to resolve the equations for separating the binary or multicomponent mixture in the second SMB; and

d) evaluating and comparing the economic efficiency of the first and second SMBs.

The ability to scan various design and operating parameters is significant not only for the design of SMBs; it has also, for the first time, led to the development of SMBs which are optimized for economic efficiency. One of the most significant parameters for influencing economic efficiency is zone length, and the present invention allows all of the components of zone length (i.e. column length, column number, or column allocation) to be readily scanned to find the column configuration of optimum economic efficiency. Thus, in still another embodiment the invention provides four zone SMBs that comprise five or more columns, and five zone SMBs that comprise six or more columns, in which the columns are allocated among zones in a manner that minimizes the desorbent use, or that maximizes the throughput through the SMB, or that balances these two criteria for optimum economic efficiency.

Using the standing wave design, the inventors have also surprisingly discovered optimal splitting strategies for separating an intermediate affinity component or fraction from a multicomponent mixture using SMB chromatography, including strategies that had not heretofore been considered. In particular, the inventors have discovered that when only the intermediate fraction is desired in high purity from a multicomponent fractionation, the rate of desorbent consumed for a given rate of feed can be minimized by allowing one of the other fractions to distribute in the first ring while separating the intermediate fraction from the second fraction. When more than one fraction is desired in high purity, the inventors have discovered that the easiest split should be performed in the first ring, and the more

difficult split performed in the second ring. Thus, in one embodiment the invention provides methods for designing SMBs for multicomponent separations by observing the foregoing splitting rules. In another embodiment the invention provides SMBs in which when only the intermediate component or fraction is desired in high purity from a multicomponent fractionation, allowing the slower or faster fraction or component to distribute in the first ring while separating the intermediate fraction from the second fraction.

The standing wave design of the present invention can be readily applied to convert an industrial or laboratory batch chromatography process to a simulated moving bed process in order to increase the yield, purity, and throughput of the system. Stationary phase utilization (i.e. throughput) and desorbent consumption can be substantially improved over such processes by appropriate designs of zone lengths, flow rates, and port switching time. A SMB system designed for the size exclusion purification of insulin, using a Sephadex gel and consisting of two SMBs in series, achieved 99.9% purity, 99.0% yield, and 1.19 L/hr100L BV throughput.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic drawing of a four ring simulated moving bed, showing the introduction points of the feed and desorbent lines, the withdrawal points for extract and raffinate, and the direction of mobile phase and port movement.

Figure 2 is a hypothetical graph illustrating the triangular region of SMB operating conditions that assures complete separation of two components in an ideal system, where the normalized mobile phase velocity in zone II is plotted against the x-axis, and the normalized mobile phase velocity in zone III is plotted against the y-axis.

Figure 3 is a graph showing the triangular region of SMB operating conditions in zones II and III for an ideal system. Several smaller triangular regions are interposed of operating conditions derived from computer simulations of the SMB assuming various mass transfer resistances, wherein the end-purity of the components is held constant at 99%. The graph is taken from Azevedo and Rodriguez (1999). The vertex point of each triangle represents the conditions under which desorbent consumption is minimized, as determined by the standing wave analysis of Ma and Wang (1997).

Figure 4 is a list of parameters involved in the design of an SMB process. The relations among these parameters are also shown in this figure.

Figure 5 is a concentration profile of the standing concentration waves in a continuous moving bed for separating two components in a non-ideal system. Solute 1 is the fast moving solute; solute 2 is the slow moving solute.

Figures 6a and 6b are concentration profiles of the standing concentration waves in an SMB for separating N components without mass transfer resistances (a), and with mass transfer resistances (b), wherein solute 1 is the fastest moving solute, solute N is the slowest moving solute, and a split is desired between components j and j+1.

Figure 7 is a concentration profile showing six strategies for separating components numbered 1, 2, and 3 in the ring of an SMB, in a mixture where $a_1 < a_2 < a_3$ (i.e. the affinity of a_1 for the stationary phase is less than the affinity of a_2 for the stationary phase, and so forth), and mass-transfer resistances are neglected.

Figure 8 is a flow chart of the various parameters which go into the design of an SMB using the standing wave analysis, and how they are used to arrive at the economic efficiency of a particular SMB.

Figures 9(a)-(d) are elution chromatograms charting experimental data and computer simulation results of pulse tests with a lab scale column at various concentrations for (a) blue dextran, (b) NaCl, (c) BHI, and (d) $ZnCl_2$.

Figures 10(a)-(c) are elution chromatograms charting experimental data and computer simulations of long pulse tests employing a saturated BHI saturation solution eluted with 1 N acetic acid with a pilot-scale column, run at (a) 8.1mL/min, (b) 4.0mL/min, and (c) 2.0mL/min.

Figures 11(a)-(c) are chromatograms charting experimental data and simulation results of a multiple BHI frontal test with a lab-scale column, including multiple frontal data without a column (a), multiple frontal data with a column (b), and isotherm absorption data imposed against an anti Langmuir isotherm model (c).

Figures 12(a) and (b) present experimental data and simulation results of a) the effluent history at the raffinate port of BHI, HMWP and $ZnCl_2$, and (b) the effluent history at the extract port of BHI, HMWP and $ZnCl_2$, in an SMB process for separating BHI from HMWP and $ZnCl_2$. Figure 12c) shows mid-cycle column concentration profiles at the 45th cycle.

Figures 13(a) and (b) present experimental data and simulation results of (a) the effluent history at the raffinate port of BHI, and (b) the effluent history at the extract port of BHI, in an SMB process for separating BHI from HMWP and $ZnCl_2$. Figure 13(c) shows

mid-cycle column concentration profiles at the 45th cycle. Data are presented for five simulations in which E_b for zone III varies from the value estimated from the Chung and Wen correlation to 200 times the value estimated from the Chung and Wen correlation.

Figures 14(a) and (b) present experimental data and simulation results of a) the effluent history at the raffinate port of BHI, HMWP and $ZnCl_2$, and (b) the effluent history at the extract port of BHI, HMWP and $ZnCl_2$, in a second SMB process for separating BHI from HMWP and $ZnCl_2$. Figure 14(c) shows mid-cycle column concentration profiles at the 45th cycle.

Figures 15(a) and (b) present experimental data and simulation results of a) the effluent history at the raffinate port of BHI, HMWP and $ZnCl_2$, and (b) the effluent history at the extract port of BHI, HMWP and $ZnCl_2$, in a third SMB process for separating BHI from HMWP and $ZnCl_2$. Figure 15(c) shows mid-cycle column concentration profiles at the 61st cycle.

Figure 16 is an overlay of elution chromatograms of outlet concentration profiles resulting from single component pulse injections of sulfuric acid, glucose, xylose, and acetic acid at 10 mL/min.

Figure 17 is an elution chromatogram of the outlet concentration profiles resulting from pulse injections of a four component mixture comprising sulfuric acid, glucose, xylose, and acetic acid at 80 mL/min.

Figures 18(a)-(d) are simulated and experimental zone concentration profiles in an SMB experiment for removing sulfuric acid from glucose, xylose, and acetic acid. Zone concentration profiles are provided separately for sulfuric acid (a), glucose (b), xylose (c), and acetic acid (d).

Figures 19(a) and (b) are simulated zone concentration profiles in a two ring SMB process in which sulfuric acid is separated from a mixture of glucose, xylose, and acetic acid in the first ring (a), and acetic acid is separated from glucose and xylose in the second ring (b).

Figures 20(a) and (b) are simulated zone concentration profiles in a two ring SMB in which acetic acid is separated from glucose, xylose, and sulfuric acid in the first ring (a), glucose and xylose are separated from sulfuric acid in the second ring (b).

Figures 21(a) and (b) are simulated zone concentration profiles in a two ring SMB process in which glucose and xylose are separated from sulfuric acid in the first ring, and

acetic acid is allowed to distribute between the product ports in the first ring (a), and glucose and xylose are separated from acetic acid in the second ring (b).

Figures 22(a) and (b) are simulated zone concentration profiles in a two ring SMB process in which glucose and xylose are separated from acetic acid in the first ring, and sulfuric acid is allowed to distribute between the product ports in the first ring (a), and glucose and xylose are separated from sulfuric acid in the second ring (b).

Figures 23(a) and (b) contain column concentration profiles for the estimation of product concentrations and decay factors for components to be enriched at the raffinate port (a) and for components to be enriched at the extract port (b). Figure 23(c) represents the mixing junction at the feed port showing how the mass balance is calculated for a component of the extract in the estimation of product concentrations and decay factors.

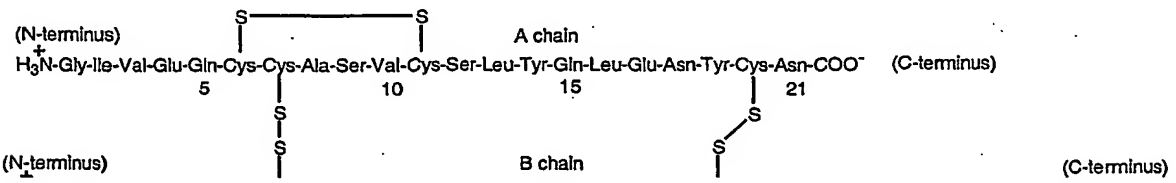
DETAILED DISCUSSION

Definitions

Chromatography -- As used herein, the term chromatography refers to any analytical technique used for the chemical separation of mixtures and components, that relies upon selective attraction among the components of a mixture for a stationary phase. Examples include adsorption chromatography, partition chromatography, ion exchange chromatography, size exclusion chromatography, and affinity chromatography.

"Adsorbent" – The term adsorbent is used herein generically to refer to the stationary phase used in chromatography for which the mobile phase components exhibit a selective affinity. Because such affinity can take a variety of forms other than adsorption (including size exclusion or complexation), the term refers to stationary phases that adsorb the components of a mixture and to stationary phases that do not technically adsorb components from the mobile phase, but which nevertheless behave as an adsorbent by slowing the migration velocity of one component relative to another in a chromatographic system.

"Insulin" -- The term insulin refers to a protein having the following amino acid sequence and structure (naturally occurring insulin), and biologically active analogues and derivatives thereof:



The term thus includes insulin which is derived from human, porcine, and bovine species, as well as insulin that is chemically synthesized or expressed using recombinant protein expression systems that use, for example, E-coli or yeast as the host. A preferred insulin is human insulin expressed using a protein expression system. Recombinant insulin will sometimes be referred to herein as biosynthetic human insulin or BHI.

An analogue of insulin means an insulin that contains one or more amino acid substitutions, deletions, additions, or rearrangements compared with human insulin at sites such that the insulin analogue still participates in the metabolism of carbohydrates when administered *in vivo*, and can be used in the treatment of diabetes mellitus. Examples of insulin analogues include LysB28, ProB29-human insulin, AspB28-human insulin, and GlyA21, ArgB31, ArgB32-human insulin.

Insulin derivatives include naturally occurring insulin and insulin analogues that are chemically or enzymatically derivatized at one or more constituent amino acids, including side chain modifications, backbone modifications, and N- and C- terminal modifications, by for example acetylation, acylation, hydroxylation, methylation, amidation, phosphorylation or glycosylation, and that retain the *in vivo* biological activity of insulin. An example of an insulin derivative is myristoyl-Nε-LysB29-human insulin.

Simulated Moving Bed – A simulated moving bed refers to a modified continuous moving bed configuration in which the movement of the adsorbent phase is simulated by the periodic movement of feed, desorbent, extract, and raffinate lines in the direction of mobile phase flow. The typical simulated moving bed contains four separate zones and at least 4 identically sized columns allocated among the zones. However, the SMB need not consist of four zones precisely. For example, the number of zones can be reduced to three if the desorbent is not regenerated, and is instead withdrawn completely in the raffinate and extract streams. Similarly, five zones can be employed to allow three streams to be withdrawn from the ring, especially where four or more components are separated in the system. As a further example, the SMB can comprise one or more regeneration zones.

Ring – The term "ring" is used to describe how the zones are configured in relation to one another in an SMB because the output of each zone comprises the input for the successive zone, in a circular fashion. The term "ring" should thus not be understood to be limited to a circular configuration of the zones and columns within the zones.

Linear Isotherms -- A system that exhibits linear isotherms refers to a system in which the partition coefficient of component i (*i.e.* the ratio of the concentration of component i in the mobile phase divided by the concentration of component i in the stationary phase) is constant. Thus, in a linear system with mass transfer effects, the migration velocity of component i is governed by the following equation:

$$u_{w,i} = \frac{u_0}{1 + P\delta_i} \tag{7}$$

where $P \equiv (1 - \varepsilon_b)/\varepsilon_b$ is the mobile-phase/particle-phase volume ratio, ε_b is the interparticle void fraction, u_0 is the interstitial linear velocity, and δ_i is the retention factor of solute i:

$$\delta_i (\equiv K_{ei}\varepsilon_p + (1 - K_{ei}\varepsilon_p)a_i) \tag{8}$$

where Ke_i is the size-exclusion factor, ε_p is the particle void fraction, and a_i is the low-concentration partition coefficient on a solid-volume basis. A system exhibits linear isotherms can be well represented by the foregoing relationship. A size-exclusion system, in which the value of a_i is zero, is the simplest linear isotherm system. Weak adsorption (with values for a_i approaching zero) can be represented using an apparent Ke that has a higher value than the intrinsic Ke. Many types of chromatographic systems can be operated within a region of linear isotherms. However, some systems observe nonlinear isotherms over a larger range of operating conditions, or a larger number of feed/adsorbent combinations. Systems typically depart from linear isotherms as component concentration is increased (or absorbent capacity is decreased), and competition among the components for available adsorbent capacity becomes a factor.

Multicomponent mixture -- The term multicomponent mixture refers to a fluid mixture that comprises three or more components or fractions which can be separated using a prescribed chromatographic process, because each component or fraction displays a different affinity for the adsorbent employed.

"Purified" -- A component or fraction is said to be purified when its relative concentration (weight of component or fraction divided by the weight of all components or fractions in the mixture) is increased by at least 20%. In one series of embodiments, the relative concentration is increased by at least 40%, 50%, 60%, 75%, 100%, 150%, or 200%. A component or fraction can also be said to be purified when the relative concentration of components from which it is purified (weight of component or fraction from which it is purified divided by the weight of all components or fractions in the mixture) is decreased by at least 20%, 40%, 50%, 60%, 75%, 85%, 95%, 98%, or 100%. In still another series of

embodiments, the component or fraction is purified to a relative concentration of at least 50%, 65%, 75%, 85%, 90%, 95%, 97%, 98%, or 99%. When a component or fraction in one embodiment is "separated" from other components or fractions, it will be understood that in other embodiments the component or fraction is "purified" at the levels provided herein.

Intermediate component or fraction -- The intermediate component or fraction of a multicomponent mixture refers to the component (or fraction of components) which, in a particular chromatographic system, displays an affinity for the stationary phase that is intermediate of the affinities of at least two other components or fractions for the stationary phase. The "components" or "fractions" of a mixture do not include solvents and other materials that do not exhibit a significant affinity for the adsorbent, and are separated from the desired components after SMB processing through conventional chemical operations such as distillation.

Mass transfer effects -- Mass transfer effects refer generally to those physical phenomena which cause components of a mixture to display distinct dispersion behavior from the mixture in a given system, and to depart from the ideal system. Mass transfer effects thus include those effects modeled using axial dispersion coefficients, intraparticle diffusion coefficients, and film mass transfer coefficients. Mass transfer effects thus also include fronting and dispersion due to extra-column dead volume. A separation is hindered by non-negligible mass transfer effects if the mass transfer correction term, discussed in more detail below, is more than 2% of the mobile phase velocity in any of the zones as prescribed by equations 3-6 (the mobile phase velocities for an ideal system), to achieve a prescribed purity and yield. The designs of the present invention can also extend to systems in which the mass transfer correction velocity increases or decreases the mobile phase velocity for the ideal system by more than 1, 3, 5, 7.5, 10, 15, 20, 30, 50, 75, 100%, 200%, 400%, 600%, 1000%, or more.

Fronting and/or extra-column effects – Fronting refers to a physical phenomenon that concentration waves spread in the direction of fluid flow as a result of anti-Langmuir type of isotherm (Karger et al., 1973) or deviation from plug flow. The deviation is usually caused by non-uniform packing, viscosity effects (Flodin, 1961; Collins, 1961), etc. Extra-column effects refer to the effects that are resulted from extra-column dead space including connecting tubing, sampling lines, void space of column heads. The extra-column effects result in a delay in solutes travelling through a chromatographic system and also result in

concentration wave spreading in addition to the spreading caused by the aforementioned intra-column mass transfer effects.

Separation -- A first component or fraction is said to be separated from a second component or fraction when the weight ratio of the second component or fraction to the first component or fraction is reduced by at least 50%. The ratio is preferably reduced by at least 65%, 75%, 85%, 90%, 95%, 98%, or 99%.

"First" -- In a number of contexts, a numeric identifier such as first or second is used to describe a particular element of a system or method. It should be understood that the numeric identifier is used simply for drafting convenience, and should not be interpreted to imply the existence of a second from the presence of a first. Thus, reference to a first ring allows for the presence of a second ring, but does not imply such presence. Similarly, where first and second things are prescribed, such as first and second stationary phases of two tandem rings, it is to be understood that these two things may be the same (such as the same type of absorbent), but that the things are distinct in a spatial or other separative sense.

"Resolving an equation" – In a number of instances herein, a set of operating conditions and/or design parameters are specified, and it is indicated that equations that relate these operating condition or design parameters are resolved to arrive at the SMBs of the present invention. When such a relationship is defined, it will be understood that the relationship is not literally restricted by the exact operating conditions and/or design parameters defined by the set, but that the equations can also be resolved using variables from which the operating conditions and/or design parameters can be derived. For example, in a number of embodiments, equations are provided that relate product purity and yield to various other terms. It will be understood that such equations might also relate purity of the separated components in the extract and raffinate, because product purity and yield can be readily derived from such purities. Thus, when a particular equation is given for designing the SMBs of the present invention, and it is indicated that a derivative of the equation can also be employed, it will be understood that such derivatives include substitution of variables for which a known relationship exists, by integrating such relationships into the equations. Similarly, when an equation is resolved or a separation is performed based upon a defined parameter, it will be understood that the equation can be resolved, or the separation achieved, based upon another specified parameter if the value of the defined parameter can be derived from such specified parameter.

"Optimize economic efficiency" -- On several occasions it is noted herein that the economic efficiency of SMBs can be improved or optimized using the methods of the present invention. It will be understood that the ultimate economic efficiency of a system relies upon a set of interrelationships that are too numerous to be expressed herein adequately, but which generally can be assessed based upon commonly known methods in chemical engineering design. Economic efficiency can often be judged by rules of thumb for a particular system. For example, in many systems the economic efficiency can be judged strictly by throughput, because the capital and maintenance costs associated with throughput predominate. In other systems, the economic efficiency can be judged by the amount of desorbent used, due to the cost of separating the desorbent from the desired component(s), or the raw material cost of the desorbent. Thus, in preferred embodiments of this invention the economic efficiency is based upon the rate of throughput or the desorbent use. Such rates and ratios, as with any other rates and ratios expressed herein, are volumetric unless expressly stated otherwise herein, or unless the context clearly requires otherwise.

When the throughput or desorbent use for a particular system is "optimized," it will be understood that the throughput approaches or equals the maximum level obtainable under standing wave conditions, or that the desorbent use approaches or equals the minimum desorbent use obtainable under standing wave conditions, for the particular system being investigated. Thus, throughput is maximized if it exceeds 85%, 90%, 95%, 97%, 98%, or 99% of the standing wave maximum. Desorbent use is minimized if it is less than 125%, 115%, 110%, 105%, 103%, 102%, or 101% of the standing wave minimum.

Desorbent -- The term desorbent means the mobile phase which is added to a SMB ring between the raffinate and extract ports. The term "desorbent" is used because, when combined with the total mobile phase, the desorbent contributes to the desorption waves of the various components in their respective zones, whether by increasing the mobile phase velocity in a size exclusion system, or by physically displacing or removing the solution from the solid phase. Thus, the term "desorbent" is not meant to imply that the desorbent composition has any particular desorbent capacity, or that it desorbs through any particular physical mechanism.

"Desorbent use" - - The term desorbent use refers to the volumetric flow rate of desorbent into a SMB, and can thus be measured directly at the desorbent inlet line. Desorbent use is minimized if, for a given separation in a defined system, desorbent use is

less than 125%, 115%, 110%, or 105% of the theoretical desorbent use defined by the standing wave equations. The desorbent use is preferably less than 102% or 101% of the theoretical use.

Multicomponent Linear Separations

As mentioned above, the inventors have surprisingly discovered the standing wave design parameters for separating slow and fast moving components or fractions from any multicomponent mixture (containing three or more components) using SMB chromatography, under conditions that minimize desorbent consumption for a given rate of feed when linear isotherms and non-negligible mass transfer resistances are observed. The methods can be used to achieve pseudo-binary separations of multicomponent mixtures, as well as separations of intermediate affinity components and/or fractions from multicomponent mixtures. In the case of a pseudo-binary split, the desired component or fraction of a mixture will be the fastest or the slowest of a multicomponent mixture, and will be separated from the other component or fraction in one separation step, using only one SMB ring. In the case of an intermediate component or fraction purification, the intermediate component or fraction will need to be separated from the faster and slower components or fractions in two successive separations, using two SMB rings.

Thus, in one embodiment, the invention provides a process for chromatographically separating a desired component or fraction from a multicomponent mixture, under linear isotherm conditions wherein non-negligible mass transfer resistances are observed, comprising:

a) providing a simulated moving bed that comprises a first ring and a first desorbent stream;

b) providing a first feed stream that comprises the desired component or fraction and a first component or fraction;

c) introducing the first desorbent stream and the first feed stream to the first ring under conditions sufficient to separate the desired component or fraction from the first component or fraction, and to minimize desorbent use; and

d) withdrawing the desired component or fraction as a raffinate or extract from the SMB, separated from the first fraction or component.

If the process is used to separate an intermediate affinity component or fraction from a multicomponent mixture using SMB chromatography, the method will further comprise:

a) introducing a second desorbent stream and the desired component or fraction from the first ring to a second ring, under conditions sufficient to separate the desired component or fraction from the second component or fraction, and to minimize the second desorbent use; and

b) withdrawing from the second ring an extract or raffinate that comprises the desired component or fraction separated from the second component or fraction.

The SMBs designed according to the present invention can be optimized in a number of respects according to the various optimization strategies discussed herein. For example, as discussed more fully elsewhere herein, the SMBs can be designed to assure that columns are allocated among zones in a manner that maximizes economic efficiency, or to assure that the splitting sequence employed is the most economical. Moreover, the methods can be readily adapted to accommodate extra-column effects and/or non-ideal flow effects such as fronting.

A particularly important feature of the SMBs of the present invention, however, is their optimal balance of desorbent use and raw material feed for a given system. In other words, desorbent use is minimized for a given rate of feed, and the rate of feed is maximized for a given rate of desorbent use. In order to understand why the present SMBs display these optimum operating characteristics, one must first understand the standing wave theory that goes into their design.

The design methods of the present invention are preferably performed in a computer environment. For example, the system is preferably designed by inputting one or more design or operating parameters into a machine in which equations that govern the SMB are encoded, and obtaining from the machine an output that defines one or more other design or operating parameters. Moreover, the design method is typically followed by the step of performing an SMB separation (either experimentally or using a computer simulation) under the conditions determined by the design. However, in some situations it may be beneficial to adjust the flow rates determined by the design, in which case one would relax the standing wave conditions determined by the design in one or more of the zones, before performing the separation. The following is an explanation of the method and its theoretical underpinnings.

In a four-zone SMB, the function of each zone is as follows: (1) Zone I: This zone is located between the desorbent inlet and extract withdrawal and used for desorbing the slow

fraction. A portion of the stream leaving this zone is withdrawn as the extract while the remainder flows into zone II. (2) Zone II: This zone is used for desorption of the fast fraction and separation from the slow fraction. (3) Zone III: This zone is used for the separation of the slow fraction from the fast fraction. The fast fraction is partially withdrawn at the raffinate port. (4) Zone IV: This zone is used for adsorption of the fast fraction as well as desorbent recovery. The stream leaving this zone should ideally contain only pure desorbent which is recirculated to the desorbent inlet for reuse.

In order to have stable continuous operation in a four zone SMB, the flow rates in the four zones must satisfy the following conditions:

$$F^{I} > F^{II} \tag{9}$$

$$F^{II} < F^{III} \tag{10}$$

$$F^{III} > F^{IV} \tag{11}$$

$$F^{IV} < F^{I} \tag{12}$$

In addition, in order for two components to separate, the migration velocities of the two components must be taken into account to determine the zone flow rates. The following conditions for the velocities in each zone are known from the literature (Ruthven and Ching, 1989; Wankat, 1994).

$$u_{s2}^{III} - v < 0 \tag{13}$$

$$u_{s1}^{IV} - v < 0 \tag{14}$$

$$u_{s2}^{I} - v > 0 \tag{15}$$

$$u_{s1}^{II} - v > 0 \tag{16}$$

where v is the average port movement along the direction of the desorbent flow, and u_{s2}^{I} and u_{s2}^{III} are the linear migration velocities of component 2 in zones I and III, respectively. The same convention is used for component 1 in zones II and IV. Equations 13 and 14 indicate that the migration velocity of the slow fraction (component 2) should be less than v in zone III and that of the fast fraction (component 1) should be less than v in zone IV. Equations 15 and 16 indicate that the velocity of component 2 should be greater than v in zone I and that of component 1 should be greater than v in zone II. Equations 13-16 define all the feasible zone flow rates and the port movement velocities needed to guarantee separation. These equations must be satisfied in order to have separation for systems with or without mass-transfer resistances.

Within the stability region defined in equations 13-16, there are infinite combinations of zone flow rates and port movement velocities (switching times) that guarantee separation in a given system. Among these, the optimal zone flow rates and port movement velocity that give the highest throughput and the lowest desorbent consumption for a multicomponent mixture can be found by selecting the proper concentration waves to remain standing in each zone (i.e. the standing wave analysis). Figure 6a illustrates, for a system without mass transfer effects, which waves must remain standing in each zone to assure complete separation of two fractions in a multicomponent system.

In particular, Figure 6a shows that:

(1) in zone I, the desorption wave of the slowest moving component (component N) must remain standing;

(2) in zone II, the desorption wave of component j must remain standing;

(3) in zone III, the adsorption wave of component j+1 must remain standing; and

(4) in zone IV, the adsorption wave of the fastest moving component (component 1) must remain standing.

It has been proven experimentally, and set forth in the examples herein, that the foregoing conditions assure that a desired separation is achieved in an SMB. The standing wave conditions associated with the separation depicted in Figure 6a can be expressed algebraically by the following equations:

$$u_0^{\mathrm{I}} = (1 + P\delta_N)\nu \tag{17}$$

$$u_0^{\mathrm{II}} = (1 + P\delta_j)\nu \tag{18}$$

$$u_0^{\mathrm{III}} = (1 + P\delta_{j+1})\nu \tag{19}$$

$$u_0^{\mathrm{IV}} = (1 + P\delta_1)\nu \tag{20}$$

wherein the port movement velocity is given by

$$\nu = \frac{F^{feed}}{SP\varepsilon_b(\delta_{j+1} - \delta_j)} \tag{21}$$

N represents the number of components in the system, numbered from low to high affinity as

$$1, \ldots, j, j+1, \ldots, N$$

and in which a split is desired between component j and j+1. u_0 is the interstitial velocity of the mobile phase, and the u_0 determined by equations 17-21 represents what is termed herein the "ideal mobile phase velocity." The remaining terms are defined as follows: S is the column cross sectional area; $\delta_i(\equiv K_{ei}\varepsilon_p + (1-K_{ei}\varepsilon_p)a_i)$ is the retention factor for linear systems (a_i is the partition constant between the adsorbed phase and the liquid phase for component i at an infinitesimal concentration, and ε_p is the porosity of the particle); K_{ei} is the size **exclusion** factor for component i for the packing material used in the SMB. $P(\equiv \frac{1-\varepsilon_b}{\varepsilon_b})$ is the bed phase ratio; ε_b is the interstitial bed void fraction; and F^{feed} is the feed flow rate. The variables a_i, ε_p, K_{ei}, and ε_b are intrinsic engineering parameters that can be estimated from elution chromatograms or, for some systems and packing materials, may be taken from the literature or manufacturer's specifications.

Once the intrinsic engineering parameters are known, and an initial column cross section is selected, one can readily derive the four zone flow rates and the port movement velocity for a given F^{feed}, because there are five equations, equations 17-21, with five unknowns, u_0^I, u_0^{II}, u_0^{III}, u_0^{IV}, and ν.

Conversely, the equations can be solved based upon a given rate of desorbent consumption, using equation 22:

$$\frac{F^{des}}{\varepsilon_b S} = u_0^I - u_0^{IV} \tag{22}$$

wherein F^{des} is the desorbent flow rate. Taking this approach, one can identify the highest feed rate for a given desorbent consumption rate, because u_0^{III} is the highest and u_0^{II} is the lowest among all of the feasible designs that guarantee separation.

Of course, if a pseudo-binary split is contemplated, in which the desired component is the fastest or slowest component of a multicomponent mixture, then equations 17-20 would need to be appropriately modified. In particular, if the desired component was the fastest component, then the retention factor of component 1 would be used to determine the mobile phase in zone II. Alternatively, if the desired component was the slowest component, the retention factor of component N would be used to determine the mobile phase velocity in zone III.

Because desorbent consumption and feed rate are two of the principle factors that determine system cost and efficiency, the ability to quickly identify maximum feed rates for a given desorbent use, or minimum desorbent use for a given feed rate, using the foregoing equations, allows one to quickly and efficiently scan various desorbent/feed ratios and determine system parameters that optimize the economic efficiency of the system. This is especially true in the ideal systems governed by the above operating parameters, in which 100% product yield is assumed.

Mass Transfer Resistances

The foregoing discussion has thus far been limited to the design of ideal systems in which there are no significant mass transfer resistances. Because there is no dispersion of components within the zones, pure products at both output ports can be obtained for any zone length and without any limit on feed flow rate or throughput. Theoretically, the feed flow rate can be as high as the equipment allows. This is illustrated by the perpendicular concentration waves in Figure 6a. Because the concentration waves are perpendicular, zone lengths can be compressed and components will not migrate unwittingly from one zone to the next.

By contrast, for non-ideal systems (i.e. systems with mass transfer resistances), there exists a maximum feed flow rate that is a function of zone lengths, product purities desired, isotherms, and mass-transfer parameters. Figure 6b illustrates this point. As shown in Figure 6b, mass transfer effects cause concentration waves to spread through their respective zones (i.e. the waves are no longer perpendicular). Moreover, if the concentration waves are not confined they will cause contamination at the extract and raffinate ports.

The waves can be confined to their respective zones, and pure products obtained at the extract and raffinate ports, by increasing the zone lengths, or altering the velocities of port movement and of the mobile phase. However, some degree of contamination is typically acceptable and even desirable from an economic standpoint. Thus, the SMB can also be designed to allow for a particular degree of contamination, and to allow a more economical operation of the SMB.

The SMBs of the present invention can be designed to accommodate systems in which separation is hindered by non-negligible mass transfer resistances, regardless of which mass transfer mechanism or mechanisms predominate, by an extension of the

foregoing standing wave concepts to non-ideal systems. In particular, to design a system with significant mass-transfer resistances (non-ideal systems), equations 17-21 are modified by correction terms to account for the wave spreading of the components whose concentration waves are kept standing in each zone, attributable to the mass transfer effects. The complete solutions of the linear velocities for multicomponent separation in the four zones in a SMB, corrected for the effects of mass transfer, can be found from equations 3-6, based on the concept of standing waves (Figure 6b).

$$u_0^{\mathrm{I}} = (1+P\delta_N)\nu + \beta_N^{\mathrm{I}}\left(\frac{E_{b,N}^{\mathrm{I}}}{L^{\mathrm{I}}} + \frac{P\nu^2\delta_N^{\,2}}{K_{f,N}^{\mathrm{I}}L^{\mathrm{I}}}\right) \tag{3}$$

$$u_0^{\mathrm{II}} = (1+P\delta_j)\nu + \beta_j^{\mathrm{II}}\left(\frac{E_{b,j}^{\mathrm{II}}}{L^{\mathrm{II}}} + \frac{P\nu^2\delta_j^{\,2}}{K_{f,j}^{\mathrm{II}}L^{\mathrm{II}}}\right) \tag{4}$$

$$u_0^{\mathrm{III}} = (1+P\delta_{j+1})\nu - \beta_{j+1}^{\mathrm{III}}\left(\frac{E_{b,j+1}^{\mathrm{III}}}{L^{\mathrm{III}}} + \frac{P\nu^2\delta_{j+1}^{\,2}}{K_{f,j+1}^{\mathrm{III}}L^{\mathrm{III}}}\right) \tag{5}$$

$$u_0^{\mathrm{IV}} = (1+P\delta_1)\nu - \beta_1^{\mathrm{IV}}\left(\frac{E_{b,1}^{\mathrm{IV}}}{L^{\mathrm{IV}}} + \frac{P\nu^2\delta_1^{\,2}}{K_{f,1}^{\mathrm{IV}}L^{\mathrm{IV}}}\right) \tag{6}$$

The right side of equations 3-6 is the mass transfer correction term for each zone, which establishes the extent to which the "ideal mobile phase velocity" must be altered in each zone to accomplish a desired level of separation. The mass transfer correction factors account for wave spreading by the components retained (or released) in each zone. As mentioned previously, the mobile phase velocity which is allowable in each zone is a function of zone lengths, product purities desired, isotherms and mass-transfer parameters. Isotherms are accounted for through the retention factor for the mass center velocity for each concentration wave that remains standing in the four zones. The remaining factors are associated exclusively with mass transfer, and are taken into account by the mass transfer correction term for each concentration wave that must remain standing in the four zones.

Thus, L is the zone length, E_b is the axial dispersion coefficient, K_f is the lumped mass-transfer coefficient, β is related to the ratio of the highest concentration to the lowest concentration of the standing wave in a specific zone (Figure 6b), and the remaining terms are as defined above. Once again, the intrinsic engineering parameters E_b and K_f can be determined experimentally by small pulse or large pulse elution chromatograms, or in some

systems by reference to the literature. Alternatively, the lumped mass-transfer coefficient, $K_{f,i}{}^m$, for component i in zone m can be calculated from the following equation:

$$\frac{1}{K_{f,i}{}^m} = \frac{R_p{}^2}{15 K_{e,i}\, \varepsilon_p\, D_{p,i}} + \frac{R_p}{3 k_{f,i}{}^m} \tag{23}$$

This parameter lumps the effects of film mass transfer and pore diffusion into a single term (Ruthven, 1984). The film mass transfer coefficient (k_f) can be estimated from literature correlations (e.g. Wilson and Geankoplis, 1966). The pore diffusivity (D_p) is estimated from pulse tests (Wooley et al., 1998; Wu et al., 1998).

The β terms are the index of product purity and yield, and ultimately determine the overall purities and yields of products at the extract and raffinate ports. Because of their relationship to concentration gradients within a particular zone, the β terms are sometimes referred to herein as "decay coefficients." The β terms are derived solely as a function of component concentrations within particular zones. β_2^{III}, for example, is the natural logarithm of the ratio of the concentration at the inlet to zone III ($Cs_{\max}$) to that at the raffinate port for component 2 (Figures 5 and 24). The higher the β_2^{III} value, the higher the product purity of component 1 in the raffinate and the higher the yield of component 2 in the extract. To achieve high yield of component 1 in the raffinate and high purity of component 2 in the extract requires a high β_1^{II} value. To ensure high purity and high yield of both components, both high β_2^{III} and β_1^{II} values are needed.

The parameter β_i^m is thus defined algebraically as follows:

$$\beta_i{}^m \equiv \ln\left(\frac{C_{i,\max}{}^m}{C_{i,\min}{}^m}\right) \tag{24}$$

where $C_{i,\max}{}^m$ represents the time-averaged maximum concentration of component i in zone m.

β values can be derived with knowledge of the purity and yield of one of the components to be separated in a two component system, or with knowledge of the yield of all components (or fractions) in an N component system. Alternatively, β values can be derived with knowledge of the purity of the two components to be separated through mass balance analyses, because knowledge of the purity of the two components to be separated

confers knowledge of purity and yield of both of the components to be separated, and vice versa.

A detailed method of determining the decay coefficients for each component is provided in the examples hereto. For many systems, however, an approximate β value will suffice. The β values can be approximated by assuming that the concentration of component 1 at the raffinate port is the same as that at the inlet to zone III (c_1^{III}) (i.e., zone III is assumed to be almost saturated). Also, the concentration ratio of the two components at the inlet of zone III (c_1^{III}/c_2^{III}) can be assumed to be the same as the ratio in the feed. If the components have the same feed concentrations and $\beta_2^{III} = \beta_1^{II}$, the purity should be the same for both products.

In order to have a physically meaningful solution for v, the following equation (25) must be satisfied:

$$P^2(\delta_{j+1}-\delta_j)^2 - 4\left(\frac{P\beta_{j+1}^{\text{III}}\delta_{j+1}^{2}}{K_{f,j+1}^{\text{III}}L^{\text{III}}} + \frac{P\beta_j^{\text{II}}\delta_j^{2}}{K_{f,j}^{\text{II}}L^{\text{II}}}\right)\left(\frac{F^{feed}}{\varepsilon_b S} + \frac{\beta_{j+1}^{\text{III}}E_{b,j+1}^{\text{III}}}{L^{\text{III}}} + \frac{\beta_j^{\text{II}}E_{b,j}^{\text{II}}}{L^{\text{II}}}\right) \geq 0 \quad (25)$$

From equation 25, if the lengths of zones I through IV are known, the maximum β values can be obtained by letting F^{feed} equal zero. If β values are fixed, the maximum F^{feed} can be obtained by letting the left side of the equation equal zero. Once again, it should be noted that the F^{feed} determined from these equations defines the lowest desorbent flow rate for the F^{feed} because u_0^{IV} is the highest and u_0^{I} is the lowest among all the feasible designs that guarantee separation.

If product purities (i.e. the purity of the split components in the extract and raffinate), column cross sectional area (S), zone lengths, and feed flow rate are specified, equations 3-6 can be used to find the four linear velocities and the port movement velocity. These equations define the standing wave conditions when both E_b and K_f are significant. Also, they define the maximum linear velocities for zones III and IV and the minimum linear velocities for zones I and II for a system with linear isotherms. Any lower velocities in zone III and IV and higher velocities in zone I and II result in better than specified product purities and recoveries. However, such designs will have lower throughput or higher desorbent consumption than the standing wave design.

These equations can also be used to find either the maximum throughput or the minimum desorbent consumption. Throughput and desorbent consumption are defined in the following equations:

$$Throughput = \frac{F^{feed}}{BV} \tag{26}$$

$$Desorbent\ \ consumption = \frac{F^{des}}{F^{feed} c_i^{feed}} = \frac{\gamma}{c_i^{feed}} \tag{27}$$

where BV is the total bed volume, c_i^{feed} is the concentration of component i (product) in the feed, and γ is the ratio of desorbent flow rate to feed flow rate. The higher the feed flow rate, the higher the throughput. The higher the ratio of desorbent flow rate to feed flow rate, the higher the desorbent consumption.

Once again, if a pseudo-binary split is contemplated, in which the desired component is the fastest or slowest component of a multicomponent mixture, then equations 1-6 would need to be appropriately modified. In particular, if the desired component was the fastest component, then the mass transfer correction term for component 1 would be used to determine the mobile phase in zone II. Alternatively, if the desired component was the slowest component, the mass transfer correction term for component N would be used to determine the mobile phase velocity in zone III.

The foregoing discoveries thus provide a number of general methods used in the design of simulated moving beds that support distinct, independent embodiments of the present invention. All of these methods can be used to arrive at a hypothetical SMB design, which can be used in the operation or computer simulation of an SMB.

Thus, in one embodiment the invention provides a method of designing an SMB for separating a desired fraction or component from a first fraction or component, in a multicomponent mixture of components numbered 1 . . . j, j+1, . . . N, from lowest to highest affinity, comprising:

a) providing equations that relate the design, operating, and intrinsic engineering parameters of a SMB that displays linear isotherms, wherein the equations assume standing wave conditions for the SMB;

b) prescribing a first set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to solve the equations for resolving the multicomponent mixture in a first SMB; and

c) resolving the equations.

In a four zone multicomponent separation the equations preferably assume the following standing wave conditions: in zone I: the desorption wave of component *N*, in zone II: the desorption wave of component *j*; in zone III: the adsorption wave of component *j*+1; and in zone IV: the adsorption wave of component 1; wherein the components are numbered 1 . . . *j*, *j*+1, . . . *N* in order of increasing affinity for the stationary phase, and a split is desired between components *j* and *j*+1. In a five zone SMB the standing wave conditions for the first ring described in strategy S6 in Tables 1 and 2 is preferably observed (when a split is desired between components *j* and *j*+1 is desired). In a two ring SMB, the standing wave conditions set forth for strategies S1-S6 in Tables 1 and 2 are preferably observed.

The concentration waves remain standing in the sense that the adsorption waves and desorption waves in the system, when plotted in a two dimensional graph that relates component concentrations to bed position (see, Figure 6b), are assumed to remain standing as if in a continuous moving bed. In reality, the waves will migrate at a continuous rate into the successive zone until brought back to their respective zones by a port movement. Generally speaking, however, it has been determined experimentally and by using computer simulations that increasing the frequency of movement, and increasing the number of columns in the separation zones (zones I and II), overcomes this problem.

From an algebraic standpoint, the waves remain standing in the sense that the equations define an ideal mobile phase velocity and port movement velocity for a given rate of feed, modified to account for wave spreading due to mass transfer effects. In zones I and II, the mobile phase velocity is increased to compensate for the wave spreading, and in zones III and IV, the mobile phase velocity is decreased to compensate for the wave spreading.

As mentioned above, one of the primary advantages of the present invention is the ability simply to resolve a set of algebraic equations to identify all of the operating parameters of an SMB, including the minimum desorbent use. Thus, in yet another embodiment the invention provides a method of designing an SMB for separating a desired fraction or component from a first fraction or component, in a multicomponent mixture, comprising:

a) providing equations that relate the design, operating, and intrinsic engineering parameters of a SMB that displays linear isotherms,

b) prescribing a first set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to solve the equations for resolving the multicomponent mixture in a first SMB; and

c) resolving the equations;

wherein the equations define the minimum rate of desorbent use for a given rate of feed.

Fronting and Extra-Column Effects

The SMBs of the present invention can also be designed to accommodate fronting and extra-column effects, in addition to intra-column mass transfer effects. Thus, in another embodiment the separations achieved in the various methods of this invention are hindered by non-ideal flow effects such as non-negligible fronting and/or extra-column effects (see Definitions section for explanation). Separation is hindered by fronting and/or extra-column effects if such effects would cause significant contamination among zones, but for the design of the system to account for the effects. In numeric terms, extra-column effects are considered non-negligible if, when assessed according to the methods prescribed below, they cause δ_i for a standing wave in any zone to change by more than 1%, 2%, 5%, 10%, or 20% from the value it would have assumed but for the extra-column effects. Fronting and/or extra-column effects are also considered non-negligible if, when assessed according to the methods prescribed below, they cause the mass transfer correction term for the standing wave of component i in any zone to change by more than 1%, 5%, 20%, 50%, 200%, or 1000% from the value it would have assumed but for the fronting and/or extra-column effects.

To design systems with significant fronting and extra column dead volume, equations 1-6 can be suitably modified to take into account the increase in wave retention time and additional wave spreading caused by these phenomena. The increase in retention time in linear systems can be taken into account by adding the time for a wave to go through the extra-column dead volume to the retention factor δ. For size exclusion systems a modified retention factor δ_i^* can be used as follows:

$$\delta_i^* = Ke_i\varepsilon_p + (1-\varepsilon_p)a_i + \frac{V_{CSTR}^*}{P} \tag{28}$$

$$V_{CSTR}^* = \frac{V_{CSTR}}{L_c S \varepsilon_b} \tag{29}$$

where u_0 is the interstitial velocity, S is the column cross sectional area, V_{CSTR} is the extra-column dead volume of each column (which can be modeled as a continuous stirred tank reactor), $P(\equiv \frac{1-\varepsilon_b}{\varepsilon_b})$ is the bed phase ratio, ε_b is the interstitial bed void fraction, ε_p is the intraparticle void fraction, and L_c is the column length.

The additional wave spreading due to dispersion in extra-column dead volume or fronting can be taken into account by multiplying by a factor f the intra-column dispersion coefficient E_b in each zone, which is estimated from a literature correlation of Chung and Wen (1968) for flow in a uniformly packed column. This factor can be estimated from batch chromatography data or from SMB data. This factor can range from unity in a pilot scale SMB from U.S. Filter, to as high as 200 in some SMBs from AST (Advanced Separation Technologies).

Thus, fronting and extra-column effects in a four zone SMB can be taken into account by the following equations:

$$u_0^I - (1+P\delta_N^*)v = \beta_N^I\left(\frac{f^I E_{b,N}^I}{L^I} + \frac{Pv^2\left(\delta_N^*\right)^2}{K_{f,N}^I L^I}\right) \tag{30}$$

$$u_0^{II} - (1+P\delta_j^*)v = \beta_j^{II}\left(\frac{f^{II} E_{b,j}^{II}}{L^{II}} + \frac{Pv^2\left(\delta_j^*\right)^2}{K_{f,j}^{II} L^{II}}\right) \tag{31}$$

$$u_0^{III} - (1+P\delta_{j+1}^*)v = -\beta_{j+1}^{III}\left(\frac{f^{III} E_{b,j+1}^{III}}{L^{III}} + \frac{Pv^2\left(\delta_{j+1}^*\right)^2}{K_{f,j+1}^{III} L^{III}}\right) \tag{32}$$

$$u_0^{IV} - (1+P\delta_1^*)v = -\beta_1^{IV}\left(\frac{f^{IV} E_{b,1}^{IV}}{L^{IV}} + \frac{Pv^2\left(\delta_1^*\right)^2}{K_{f,1}^{IV} L^{IV}}\right) \tag{33}$$

In general, the factor f can take into account the dispersion due to fronting, tailing, or other non-ideal flow effects.

Splitting Strategies

As mentioned above, the splitting strategy used for a particular system must be selected before the design of a multicomponent SMB separation for an intermediate component can be completed. However, without splitting rules to dictate the splitting sequence, the process of trial and error selection of operating parameters is substantially

complicated, because each of the various designs must be simulated for each of the splitting strategies. Surprisingly, the design parameters of the present invention have lead to (1) novel splitting strategies for multicomponent systems, and (2) a set of rules for determining optimal splitting strategies, based upon the relative ease of splitting the various components, and the number of pure components that are desired from a particular system.

The methods of the present invention also encompass various splitting strategies which can be employed in the purification of insulin when it is the intermediate affinity component of a multicomponent mixture. When two 4-zone SMB units are operated in series, there are several splitting strategies that can be taken to obtain purified products. In Figure 7, four such strategies (S1-S4) are shown for separating components numbered 1, 2, and 3, in a mixture where the order of retention is as follows: $a_1 < a_2 < a_3$.

In this preliminary analysis mass-transfer resistances are neglected (a case referred to as the "ideal" case) and the wave fronts are assumed to be sharp. For convenience, the standing waves shown in Figure 7 for different strategies are summarized in Table 1a. The numbers listed in Table 1 represent the standing components in each zone. For example, 3 means component 3 is standing in the associated zone.

Table 1a. Standing Waves for Various Splitting Strategies of Three Component System

	Standing Waves								
Strategy	Zone IA	Zone IIA	Zone IIIA	Zone IVA	Zone VA	Zone IB	Zone IIB	Zone IIIB	Zone IVB
S1	3*	1*	$2^{\dagger}$	$1^{\dagger}$		3*	2*	$3^{\dagger}$	$2^{\dagger}$
S2	3*	2*	$3^{\dagger}$	$1^{\dagger}$		2*	1*	$2^{\dagger}$	$1^{\dagger}$
S3	2*	1*	$2^{\dagger}$	$1^{\dagger}$		3*	2*	$3^{\dagger}$	$2^{\dagger}$
S4	3*	2*	$3^{\dagger}$	$2^{\dagger}$		2*	1*	$2^{\dagger}$	$1^{\dagger}$
S5	3*	2*	1*	$2^{\dagger}$	$1^{\dagger}$	3*	2*	$3^{\dagger}$	$2^{\dagger}$
S6	3*	2*	$3^{\dagger}$	$2^{\dagger}$	$1^{\dagger}$	2*	1*	$2^{\dagger}$	$1^{\dagger}$

* Desorption wave
† Adsorption wave

In Figure 7a, component 1 is split from 2 and 3 in the first SMB unit (ring A), and the extract product (which contains unresolved components 2 and 3) is fed to a second SMB unit (ring B), in which component 2 is split from component 3. Figure 7b is similar: component 3 is split from 1 and 2 in ring A, and 1 is split from 2 in ring B.

An N component system in which purified component j was desired would observe similar splitting strategies, as set forth in Table 1b.

Table 1b: Standing waves for various splitting strategies for N components.

	Standing Waves								
Strategy	Zone IA	Zone IIA	Zone IIIA	Zone IVA	Zone VA	Zone IB	Zone IIB	Zone IIIB	Zone IVB
S1	N^*	$j-1^*$	$j^\dagger$	$1^\dagger$		N^*	j^*	$j+1^\dagger$	$j^\dagger$
S2	N^*	j^*	$j+1^\dagger$	$1^\dagger$		j^*	$j-1^*$	$j^\dagger$	$1^\dagger$
S3	J^*	$j-1^*$	$j^\dagger$	$1^\dagger$		N^*	j^*	$j+1^\dagger$	$j^\dagger$
S4	N^*	j^*	$j+1^\dagger$	$j^\dagger$		j^*	$j-1^*$	$j^\dagger$	$1^\dagger$
S5	N^*	j^*	$j-1^*$	$j^\dagger$	$1^\dagger$	N^*	j^*	$j+1^\dagger$	$j^\dagger$
S6	N^*	j^*	$j+1^\dagger$	$j^\dagger$	$1^\dagger$	j^*	$j-1^*$	$j^\dagger$	$1^\dagger$

* Desorption wave
† Adsorption wave

In particular, for strategy S1, components 1 . . . j-1 would be withdrawn in the extract of the first SMB unit, and the raffinate product (which contains unresolved components j . . .N) would be fed to the second SMB unit in which component j would be separated from components j+1 . . . N. Strategy S2 is similar: components 1 . . . j would be split from components j+1 . . . N in the first ring, and components 1 . . . j-1 would be separated from component j in the second ring.

Figures 7a–b show how to obtain three pure products from a mixture of three components. In most cases, however, it is not necessary to obtain every component in high purity and high yield. When only the middle product is required in high purity and high yield, the inventors have unexpectedly determined that it may be preferable to allow one component to distribute throughout the entire SMB unit. For example, in Figure 7c, components 2 and 3 are separated from 1 in the first ring, so component 1 should be kept from the extract and collected in the raffinate; however, if components 1 and 3 are not required in high purity, then the standing wave condition in zone I can be relaxed to allow part of component 3 to "wrap around" (that is, to migrate from zone I into zone IV) and be taken with component 1 in the raffinate. Analogously, in Figure 7d, component 1 is allowed to "wrap around" so that it is withdrawn from both the raffinate and extract.

The conditions are relaxed in the sense that the component which is allowed to wrap around the SMB is not considered in the standing wave design. Thus, the standing wave equations governing a binary split of components, as set forth in Ma and Wang (1997), would govern the design of the system illustrated in Figures 7c and 7d. For the first split shown in Figure 7c, those equations are as follows:

$$u_0^I = (1+P\delta_2)v \tag{34}$$

$$u_0^{II} = (1+P\delta_1)v \tag{35}$$

$$u_0^{III} = (1+P\delta_2)v \tag{36}$$

$$u_0^{IV} = (1+P\delta_1)v \tag{37}$$

The tandem SMB for multicomponent fractionation is not limited to two 4-zone rings. When five zones are employed in the first ring of the tandem SMB system, there is increased flexibility in the design. Figures 7e-f show schematic representations of two such processes for the separation of three components. In Figure 7e component 1 is completely split from components 2 and 3 in the first SMB unit (ring A). Some of component 3 is withdrawn purified in an extract stream, and the remainder contaminates an intermediate extract stream that also contains component 2. The intermediate extract stream component (which contains unresolved components 2 and 3) is fed to a second SMB unit (ring B), in which component 2 is completely split from component 3. Figure 7f is similar: component 3 is completely split from 1 and 2 in ring A, some of component 1 is withdrawn purified in a raffinate stream, and the remainder contaminates an intermediate raffinate stream that also contains component 2. The intermediate raffinate stream is fed to the second SMB unit for separating components 1 and 2.

The standing wave equations governing the separations disclosed in figures 7e and 7f, for a N component system, modified by mass transfer correction terms (Δ) as discussed more fully below, are listed in Table 2.

Table 2a. Standing Waves and Equations for a Nine-Zone SMB with Strategy S5 (Figure 7e).

	Zone	Wave Type	Solute	*Standing Wave Equation*
Section 1	I	Desorption	N	$u_0^I = (1+P\delta_N)v + \Delta_N^I$

	II	Desorption	j	$u_0^{II} = (1+P\delta_j)\nu + \Delta_j^{II}$
	III	Desorption	j-1	$u_0^{III} = (1+P\delta_{j-1})\nu + \Delta_{j-1}^{III}$
	IV	Adsorption	j	$u_0^{IV} = (1+P\delta_j)\nu - \Delta_j^{IV}$
	V	Adsorption	1	$u_0^{V} = (1+P\delta_1)\nu - \Delta_1^{V}$
Section 2	I	Desorption	N	$u_0^{VI} = (1+P\delta_N)\nu + \Delta_N^{VI}$
	II	Desorption	j	$u_0^{VII} = (1+P\delta_j)\nu + \Delta_j^{VII}$
	III	Adsorption	j+1	$u_0^{VIII} = (1+P\delta_{j+1})\nu - \Delta_{j+1}^{VIII}$
	IV	Adsorption	j	$u_0^{IX} = (1+P\delta_j)\nu - \Delta_j^{IX}$

Table 2b. Standing Waves and Equations for a Nine-Zone SMB with Strategy S6 (Figure 7f).

	Zone	Wave Type	Solute	*Standing Wave Equation*
Section 1	I	Desorption	N	$u_0^{I} = (1+P\delta_N)\nu + \Delta_N^{I}$
	II	Desorption	j	$u_0^{II} = (1+P\delta_j)\nu + \Delta_j^{II}$
	III	Adsorption	j+1	$u_0^{III} = (1+P\delta_{j+1})\nu - \Delta_{j+1}^{III}$
	IV	Adsorption	j	$u_0^{IV} = (1+P\delta_j)\nu - \Delta_j^{IV}$
	V	Adsorption	1	$u_0^{V} = (1+P\delta_1)\nu - \Delta_1^{V}$
Section 2	I	Desorption	j	$u_0^{VI} = (1+P\delta_j)\nu + \Delta_j^{VI}$
	II	Desorption	j-1	$u_0^{VII} = (1+P\delta_{j-1})\nu + \Delta_{j-1}^{VII}$
	III	Adsorption	j	$u_0^{VIII} = (1+P\delta_j)\nu - \Delta_j^{VIII}$
	IV	Adsorption	1	$u_0^{IX} = (1+P\delta_1)\nu - \Delta_1^{IX}$

Note: Δ_i^m are positive numbers, the first subscript indicates the zone number and the second subscript indicates the solute.

To compare the alternative strategies shown in Figure 7, the standing wave equations for systems without mass-transfer resistances have been applied. Desorbent consumption is calculated and compared for each case. In the separation strategy shown in Figure 7a, for a fixed feed flow rate, F_A, a port movement velocity for the first ring, v_A, can

be calculated from equation 1. Using the differences between the standing wave flow rates, one can calculate the following:

$$F_A = PS\varepsilon_b v_A(\delta_2 - \delta_1) \tag{38}$$

$$D_A = PS\varepsilon_b v_A(\delta_3 - \delta_1) \tag{39}$$

$$E_A = PS\varepsilon_b v_A(\delta_3 - \delta_1) \tag{40}$$

where D_A is the desorbent flow rate for ring A and E_A is the extract flow rate. Combining equations 38 and 39 leads to the following:

$$D_A = \left(\frac{\delta_3 - \delta_1}{\delta_2 - \delta_1}\right) F_A \tag{41}$$

The extract from ring A is the feed to ring B, so that

$$F_B = E_A = PS\varepsilon_b v_A(\delta_3 - \delta_1) = \left(\frac{\delta_3 - \delta_1}{\delta_2 - \delta_1}\right) F_A \tag{42}$$

Using the difference between zone flow rates in the standing wave design, one can easily show that $D_B = F_B$, so that

$$D_B = \left(\frac{\delta_3 - \delta_1}{\delta_2 - \delta_1}\right) F_A \tag{43}$$

and

$$D_{\text{total}} = D_A + D_B = 2\left(\frac{\delta_3 - \delta_1}{\delta_2 - \delta_1}\right) F_A \tag{44}$$

A similar analysis can be applied to the cases shown in Figures 7b–d. The results are shown in Table 3a.

Table 3. Solvent Consumption and Product Dilution for Different Separation Strategies in Figure 7

(a)Three Components

Strategy	Ring A (*R*/*E*)	Ring B (*R*/*E*)	D_{Total}/F_A	$C_{2,product}/C_{2,feed}$	Pure Products

S1	1/2,3	2/3	$2\left(\frac{\delta_3-\delta_1}{\delta_2-\delta_1}\right)>2$	$\left(\frac{\delta_2-\delta_1}{\delta_3-\delta_1}\right)<1$	1, 2, 3
S2	1,2/3	1/2	$2\left(\frac{\delta_3-\delta_1}{\delta_3-\delta_2}\right)>2$	$\left(\frac{\delta_3-\delta_2}{\delta_3-\delta_1}\right)<1$	1, 2, 3
S3	3,1/2,3	2/3	2	1	2
S4	1,2/3,1	1/2	2	1	2
S5*	1 / 2,3	2 / 3	$1+\left(\frac{\delta_3-\delta_1}{\delta_2-\delta_1}\right)>2$	1	1, 2, 3
S6*	1,2 / 3	1 / 2	$1+\left(\frac{\delta_3-\delta_1}{\delta_3-\delta_2}\right)>2$	1	1, 2, 3

(b) *N* Components**

Strategy	Ring A (*R*/*E*)	Ring B (*R*/*E*)	D_{total}/F_A	$C_{j,product}/C_{j,feed}$	Pure Products
S1	{1,…*j*–1} /{*j*,…,*N*}	{*j*}/{*j*+1,… ,*N*}	$\frac{\delta_N-\delta_1}{\delta_j-\delta_{j-1}}+\left(\frac{\delta_N-\delta_j}{\delta_{j+1}-\delta_j}\right)\left(\frac{\delta_N-\delta_{j-1}}{\delta_j-\delta_{j-1}}\right)$	$\left(\frac{\delta_j-\delta_{j-1}}{\delta_N-\delta_{j-1}}\right)$	*j*, lower & upper cuts
S2	{1,…*j*}/ {*j*+1,…,*N*}	{1,…*j*–1} /{*j*}	$\frac{\delta_N-\delta_1}{\delta_{j+1}-\delta_{j-1}}+\left(\frac{\delta_j-\delta_1}{\delta_j-\delta_{j-1}}\right)\left(\frac{\delta_{j+1}-\delta_1}{\delta_{j+1}-\delta_j}\right)$	$\left(\frac{\delta_{j+1}-\delta_j}{\delta_{j+1}-\delta_1}\right)$	*j*, lower & upper cuts
S3	{1,…*j*–1, *j*+1,…,*N*}/ {*j*,…,*N*}	{*j*}/{*j*+1,… ,*N*}	$\frac{\delta_j-\delta_1}{\delta_j-\delta_{j-1}}+\frac{\delta_N-\delta_j}{\delta_{j+1}-\delta_j}$	1	*j*
S4	{1,…*j*}/{1 ,…*j*–1, *j*+1,…,*N* }	{1,…*j*–1} /{*j*}	$\frac{\delta_N-\delta_j}{\delta_{j+1}-\delta_j}+\frac{\delta_j-\delta_1}{\delta_j-\delta_{j-1}}$	1	*j*
S5*	{1,…*j*–1}/ {*j*,…,*N*}	{*j*}/ {*j*+1,…,*N*}	$\left(\frac{\delta_N-\delta_1}{\delta_j-\delta_{j-1}}\right)+\left(\frac{\delta_N-\delta_j}{\delta_{j+1}-\delta_j}\right)$	1	*j*, upper & lower

					cuts
S6*	{1,...j}/ {j+1,...,N}	{1,...j−1}/ {j}	$\left(\frac{\delta_N-\delta_1}{\delta_{j+1}-\delta_j}\right)+\left(\frac{\delta_j-\delta_1}{\delta_j-\delta_{j-1}}\right)$	1	j, upper & lower cuts

* In strategies S5 and S6, Ring A is a five-zone SMB and Ring B is a four-zone SMB; whereas in other strategies, both Ring A and Ring B are four-zone SMBs.
**Component j is the desired product.

One can easily see that strategies S3 and S4 lead to lower solvent consumption and lower product dilution. This is achieved at the price of obtaining only one purified product. Strategies S1 and S2 lead to higher desorbent usage and higher product dilution, but three purified products are obtained. It should also be noted that in choosing among strategies S1 and S2, lower desorbent consumption and lower product dilution are preferred. From Table 3a, one can see that if $(\delta_2 - \delta_1) > (\delta_3 - \delta_2)$, then strategy S1 should be chosen because the desorbent requirement and the product dilution are lower. If $(\delta_3 - \delta_2) > (\delta_2 - \delta_1)$, then strategy S2 should be chosen. In other words, the easier separation should be performed first if three purified products are desired.

The analysis for three-component systems can be easily extended to N-component systems; the final results are listed in Table 3b. Both strategies S1 and S2 result in product dilution (or $C_{j,\text{product}}/C_{j,\text{feed}}$ is less than unity) when $j < N$ and $j > 1$. If $j = 1$ or N, then a tandem SMB process is unnecessary because the desired product can be obtained in a single ring. In general, with N components the values of D_{total}/F_A and $C_{j,\text{product}}/C_{j,\text{feed}}$ need to be calculated for each strategy and the best strategy chosen from these. There is no difference in the values of D_{total}/F_A and $C_{j,\text{product}}/C_{j,\text{feed}}$ between strategies S3 and S4. The desorbent-to-feed ratio and the product dilution are lower for strategies S3 and S4 than for S1 and S2.

The tandem SMB for multicomponent fractionation is not limited to two 4-zone rings. When five zones are employed in the first ring of the tandem SMB system, there is increased flexibility in the design. Figures 7e-f shows schematic representations of two such processes for the separation of three components. Table 3a (strategies S5 and S6) shows a comparison of the system performance under the operating conditions shown in Figures 7e-f. An inspection of Table 3a reveals that the easier separation should be performed in the first ring to minimize solvent consumption. Neither configuration in strategies S5 and S6 has an advantage in terms of product dilution because both result in an undiluted center product. A comparison of the values of D_{total}/F_A in Table 3a suggests that a

five-zone SMB in Ring A results in a process that consumes less solvent and produces a less dilute product than a process with a four-zone SMB in Ring A. A similar analysis for three-component systems can be extended to *N*-components. The results for N-component systems are summarized in Table 3b (strategies S5 and S6).

When mass-transfer resistances are considered, the relationships are similar to those for the cases without mass-transfer resistance, but the results are dependent on column size, column configuration, and individual mass-transfer parameters. Taking the splitting strategy in Figure 7a, one could specify once again a feed flow rate F_A and from equation 1 calculate the port movement velocity, v_A. Defining a mass-transfer correction term as

$$\Delta_i^m \equiv S\varepsilon_b \frac{\beta_i^m}{L^m}\left(E_{bi}^m + \frac{P\delta_i^2 v^2}{K_{fi}^m}\right) \tag{45}$$

for component i in zone m and using equations 3-6, one can write the following:

$$F_A = PS\varepsilon_b v_A(\delta_2 - \delta_1) - \Delta_2^{\text{IIIA}} - \Delta_1^{\text{IIA}} \tag{46}$$

$$D_A = PS\varepsilon_b v_A(\delta_3 - \delta_1) + \Delta_3^{\text{IA}} + \Delta_1^{\text{IVA}} \tag{47}$$

$$E_A = PS\varepsilon_b v_A(\delta_3 - \delta_1) + \Delta_3^{\text{IA}} - \Delta_1^{\text{IIA}} \tag{48}$$

It should be noted that Δ_i^m is always positive. Next, the feed flow rate for ring B is set to E_A and equation 1 is used to calculate the port movement velocity, v_B, for the second ring. In this way, one can calculate

$$D_B = PS\varepsilon_b v_B(\delta_3 - \delta_2) + \Delta_3^{\text{IB}} + \Delta_2^{\text{IVB}} \tag{49}$$

The total desorbent usage is given by

$$D_{total} = PS\varepsilon_b v_A(\delta_3 - \delta_1) + PS\varepsilon_b v_B(\delta_3 - \delta_2) + \Delta_3^{\text{IA}} + \Delta_1^{\text{IVA}} + \Delta_3^{\text{IB}} + \Delta_2^{\text{IVB}} \tag{50}$$

Explicit analytical solutions of v_A and v_B exist but are not shown here due to space limitations. The total solvent consumption for each separation strategy is summarized in Tables 3(c) and (d). Suffice it to say that these solutions confirm that in systems with significant mass-transfer resistance, the same conclusions about splitting strategies hold (i.e., that the easier split should be performed first in the complete separation cases and that there is no significant difference in either strategy when one component is allowed to distribute among the two product ports).

Table 3 (cont'd). Solvent Consumption for the Separation Strategies in Figure 7 When Mass Transfer Resistance is Taken Into Account

(c) Three Components

Strategy	Ring A (*R/E*)	Ring B (*R/E*)	D_{total}	High-Purity Products
S1	1/2,3	2/3	$PS\varepsilon_b\nu_A(\delta_3-\delta_1)+PS\varepsilon_b\nu_B(\delta_3-\delta_2)+\Delta_3^{IA}+\Delta_1^{IVA}+\Delta_3^{IB}+\Delta_2^{IVB}$	1, 2, 3
S2	1,2/3	1/2	$PS\varepsilon_b\nu_A(\delta_3-\delta_1)+PS\varepsilon_b\nu_B(\delta_2-\delta_1)+\Delta_3^{IA}+\Delta_1^{IVA}+\Delta_2^{IB}+\Delta_1^{IVB}$	1, 2, 3
S3	3,1/2,3	2/3	$PS\varepsilon_b\nu_A(\delta_2-\delta_1)+PS\varepsilon_b\nu_B(\delta_3-\delta_2)+\Delta_2^{IA}+\Delta_1^{IVA}+\Delta_3^{IB}+\Delta_2^{IVB}$	2
S4	1,2/3,1	1/2	$PS\varepsilon_b\nu_A(\delta_3-\delta_2)+PS\varepsilon_b\nu_B(\delta_2-\delta_1)+\Delta_3^{IA}+\Delta_2^{IVA}+\Delta_2^{IB}+\Delta_1^{IVB}$	2
S5*	1 / 2,3	2 / 3	$PS\varepsilon_b\nu_A(\delta_3-\delta_1)+PS\varepsilon_b\nu_B(\delta_3-\delta_2)+\Delta_3^{IA}+\Delta_1^{VA}+\Delta_3^{IB}+\Delta_2^{IVB}$	1, 2, 3
S6*	1,2 / 3	1 / 2	$PS\varepsilon_b\nu_A(\delta_3-\delta_1)+PS\varepsilon_b\nu_B(\delta_2-\delta_1)+\Delta_3^{IA}+\Delta_1^{VA}+\Delta_2^{IB}+\Delta_1^{IVB}$	1, 2, 3

(d) *N* Components**

Strategy	Ring A (*R/E*)	Ring B (*R/E*)	D_{total}	High-Purity Products
S1	{1,…*j*–1}/ {*j*,…,*N*}	{*j*}/ {*j*+1,…,*N*}	$PS\varepsilon_b\nu_A(\delta_N-\delta_1)+PS\varepsilon_b\nu_B(\delta_N-\delta_j)+\Delta_N^{IA}+\Delta_1^{IVA}+\Delta_N^{IB}+\Delta_j^{IVB}$	*j*, lower & upper cuts
S2	{1,…*j*}/ {*j*+1,…,*N*}	{1,…*j*–1}/ {*j*}	$PS\varepsilon_b\nu_A(\delta_N-\delta_1)+PS\varepsilon_b\nu_B(\delta_j-\delta_1)+\Delta_N^{IA}+\Delta_1^{IVA}+\Delta_j^{IB}+\Delta_1^{IVB}$	*j*, lower & upper cuts
S3	{1,…*j*–1, *j*+1,…,*N*}/ {*j*,…,*N*}	{*j*}/ {*j*+1,…,*N*}	$PS\varepsilon_b\nu_A(\delta_j-\delta_1)+PS\varepsilon_b\nu_B(\delta_N-\delta_j)+\Delta_j^{IA}+\Delta_1^{IVA}+\Delta_N^{IB}+\Delta_j^{IVB}$	*j*
S4	{1,…*j*}/ {1,…*j*–1, *j*+1,…,*N* }	{1,…*j*–1}/ {*j*}	$PS\varepsilon_b\nu_A(\delta_N-\delta_j)+PS\varepsilon_b\nu_B(\delta_j-\delta_1)+\Delta_N^{IA}+\Delta_j^{IVA}+\Delta_j^{IB}+\Delta_1^{IVB}$	*j*
S5*	{1,…*j*–1}/	{*j*}/ {*j*+1,…,*N*}	$PS\varepsilon_b\nu_A(\delta_N-\delta_1)+PS\varepsilon_b\nu_B(\delta_N-\delta_j)$	*j*, lower & upper cuts

	$\{j,\ldots,N\}$		$+\Delta_N^{IA}+\Delta_1^{VA}+\Delta_N^{IB}+\Delta_j^{IVB}$	
S6*	$\{1,\ldots j\}/$ $\{j+1,\ldots,N\}$	$\{1,\ldots j-1\}/$ $\{j\}$	$PS\varepsilon_b v_A(\delta_N-\delta_1)+PS\varepsilon_b v_B(\delta_j-\delta_1)$ $+\Delta_N^{IA}+\Delta_1^{VA}+\Delta_j^{IB}+\Delta_1^{IVB}$	j, lower & upper cuts

* In strategies S5 and S6, Ring A is a five-zone SMB and Ring B is a four-zone SMB; whereas in other strategies, both Ring A and Ring B are four-zone SMBs.
**Component j is the desired product.

Embodiments Premised upon Performing the Easiest Split First: Thus, using the design approach of the present invention, it has been proven theoretically that when one desires to obtain three fractions and/or components from a multicomponent mixture in purified form, it is typically most efficient to perform the easiest split first, especially when desorbent expense is significant. Thus, in an improved embodiment the invention provides the multicomponent SMB separation processes of the present invention wherein: (a) the intermediate fraction is withdrawn in the extract of the first SMB; and (b) the difference between the affinities of the intermediate fraction and the slow fraction for the stationary phase in the first SMB is less than the difference between the affinities of the intermediate fraction and the fast fraction for the stationary phase in the first SMB. In another embodiment the invention provides the multicomponent SMB processes of the present invention wherein: (a) the intermediate fraction is withdrawn in the raffinate of the first SMB; and (b) the difference between the affinities of the intermediate fraction and the slow fraction for the stationary phase of the first SMB is greater than the difference between the affinities of the intermediate fraction and the fast fraction for the stationary phase for the first SMB.

Embodiments Premised Upon Allowing One Component to Distribute in First Ring: Using the standing wave design of the present invention, it has also been proven theoretically that an alternative splitting strategy should be observed when there is no need to obtain the slow or fast fraction in purified form. In this situation it does not matter whether the easier separation is performed first. However, it has proven beneficial to design the system without taking into consideration one of the components in the design of the first ring, and to allow one of the components or fractions to distribute between the raffinate and extract during separation. When a component distributes in the first ring of an SMB, the standing waves conditions for each zone are preferably specified as set forth in tables 1 and 2 for strategies S3 and S4.

Notably, this discovery can be used to improve upon the SMBs otherwise defined by this invention, or to support an independent embodiment. Thus, in another embodiment the invention provides a method for chromatographically purifying an intermediate affinity fraction from a multicomponent mixture, under linear isotherms, wherein non-negligible mass transfer effects are observed, comprising:

a) providing a simulated moving bed that comprises first and second rings and first and second stationary phases;

b) providing first and second desorbent streams;

c) providing a first feed stream that comprises a fast fraction or component, an intermediate fraction or component, and a slow fraction or component;

d) introducing the first desorbent stream and the first feed stream to the first ring under conditions sufficient to separate the intermediate fraction from the fast or slow fraction or component;

e) allowing the fast or slow fraction or component to distribute in the first ring;

f) withdrawing from the first ring the intermediate fraction or component separated from the fast or slow fraction or component;

g) introducing the second desorbent stream and the intermediate fraction or component from the first ring to the second ring as a second feed stream, under conditions sufficient to separate the intermediate fraction from the fast or slow fraction or component; and

h) withdrawing from the second ring the intermediate fraction or component separated from the fast and slow fractions and/or components.

These newly discovered splitting strategies can also be employed in the design of an SMB for purifying an intermediate fraction from a multicomponent mixture, in ideal and non-ideal systems. Thus, in another embodiment the invention provides a method of designing an SMB for separating an intermediate fraction from a fast fraction and a slow fraction in a multicomponent mixture, under linear isotherms, in ideal and non-ideal systems, wherein the SMB comprises first and second rings, comprising:

a) providing splitting rules which provide:

i) when only the intermediate fraction or component is purified, allowing the fast or slow fraction or component to distribute in the first ring;

ii) when the fast and/or slow fractions and/or components are purified, perform the easiest split in the first ring; and

b) selecting a splitting strategy based upon whether one or more of the fast and/or slow fractions and/or components is purified.

The foregoing splitting rules and methods can be integrated into each of the various methods of design and operation set forth herein, for separating an intermediate component using tandem rings.

Design Optimization

One of the most significant advantages of the design method of the present invention is the ability to screen with relative ease design and operating variables to arrive at a SMB that is most economically efficient. The method can be used to optimize SMB separations of binary and multicomponent mixtures. As discussed in the background section of this document, the prior art only provided equations from which one could derive the triangular region of separations for an ideal system (which in turn defined the relative velocities of port movement and mobile phase in zones II and III of the SMB). Any further design of the system to account for mass transfer effects, or to identify the minimum desorbent consumption, required one to perform lengthy and complex computer simulations or expensive experimental trials. If one then desired to screen other SMB designs by, for example, altering the column configurations, the desorbent/adsorbent combination, or the adsorbent particle sizes, to improve the efficiency of the system, one was then required to rerun the computer simulations all over, for each potential variation.

The design equations of the present invention simplify this process by several orders of magnitude, by reducing all of the variables associated with the design of an SMB to a simplified set of five equations 1 and 3-6. By resolving equations 1 and 3-6 one is able to arrive at the complete set of operating conditions for an SMB for separating multicomponent mixtures, in a non-ideal system under linear adsorption isotherms.

Thus, depending on what is known about or assumed for a particular system, one can reiteratively explore various separation strategies to find the most economic configuration, by varying any of the following parameters:

- Purity and/or Yield (if not specified)
- Mobile Phase / Stationary Phase Combination
- Splitting Strategies

- Zone Lengths
- Feed Flow Rate
- Column Length
- Particle Size

A schematic drawing that shows the interrelationship of these various parameters is contained in Figure 8. Generally speaking, one first assumes a number of design and operating parameters, performs some initial tests and calculations to determine retention and mass transfer parameters, and performs some initial calculations to determine maximum pressure drop allowable by the adsorbent (and hence maximum interstitial velocity). From these initial assumptions and determinations, one is able to perform the standing wave analysis to determine the maximum feed flow rate, maximum feed concentrations, the zone flow rates, and the port movement velocity of the SMB which will achieve a prescribed separation.

Once a base system has been evaluated, any of the design or operating parameters can be varied to determine whether other systems might be more economically efficient. The standing wave design eliminates the need to perform complex computer simulations each time any of the design or operating parameters is varied, and allows variations to be evaluated simply by iteratively resolving the standing wave equations for each choice of variables (after performing any calculations or experiments needed to derive a new set of engineering parameters). Once these iterations have been performed, one is able to compare the throughput of the system per bed volume and the rate of solvent consumption for each SMB system being evaluated. Because throughput and solvent consumption are the dominant considerations when evaluating the economic efficiency of a particular SMB system, on both an operating and capital cost basis, they can be used to screen the various systems for economic efficiency.

Thus, the invention provides several embodiments for optimizing SMBs using the design equations of the present invention, varying a number of the design parameters. In one particular embodiment the invention provides a method of optimizing a non-ideal SMB system that displays linear isotherms comprising:

a) providing equations that relate the design, operating, and intrinsic engineering parameters of an SMB;

b) prescribing a first set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to resolve the equations for a first SMB;

c) prescribing a second set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to resolve the equations for a second SMB; and

d) evaluating and comparing the economic efficiency of the two or more SMBs.

The standing wave conditions are preferably observed in the equations used in the foregoing design. Moreover, the equations preferably define the minimum desorbent use for a given feed flow rate.

As discussed above, the design parameters are preferably selected from: zone length, desorbent type, adsorbent type, adsorbent particle size, and splitting strategy, and the foregoing method can be used to screen variations in any of these design parameters. Of course, in many systems alternative splitting strategies need not be explored, because of the splitting rules already established by the present invention. Also, because the standing wave equations define the maximum feed flow rate for a given desorbent flow rate, or minimum desorbent flow rate for a given feed flow rate, the equations eliminate the need to vary the feed flow rate or the desorbent flow rate when performing the design.

With respect to zone length, it should be noted that zone length has three components: the length of columns used in the SMB, the number of columns employed, and the allocation of columns among the zones. Variability in any of these components can be explored using the design method of the present invention, as discussed more fully below.

The operating parameters integrated into the above equations are preferably selected from: zone flow rates, port movement velocity, feed flow rate, desorbent flow rate. Again, any of these parameters can be varied in the screening process of this invention to optimize the SMB.

The intrinsic engineering parameters for a nonideal system that displays linear adsorption isotherms are the mass transfer parameters and the retention parameters. As discussed above, these parameters can be well modeled and accounted for in the equations by the axial dispersion coefficient E_b and the lumped mass transfer coefficient K_f. Similarly, the retention parameters can be well represented in the equations by the term δ, because this term accounts for all retention phenomena (size exclusion and adsorption) in a linear relationship. However, it will be understood that various equations and variables are

defined in the field of chemical engineering to model the effects of mass transfer, or the relative retention of components in a linear chromatographic process, and the invention is intended to encompass all such equations and variables.

A straightforward approach to optimizing the economic efficiency of a system is set forth in the examples hereto. One of the principal features of this approach is to first determine maximum mobile phase velocity allowed by the adsorbent or the SMB equipment, because the SMB must be operated at the maximum allowable mobile phase velocity in order to maximize throughput for the system (i.e. within about 85, 90, 95, 97, 98%, or 99%, of the maximum allowable mobile phase velocity). Most adsorbents and SMB equipment (valves, columns, connectors, and pumps) have a maximum pressure limit or a maximum flow rate limit. One can calculate from the standing wave equations (equations 25 and 1-6) the max feed flow rate and the mobile phase velocities that can meet the purity requirement. The velocity in each zone should not exceed the corresponding maximum velocity calculated from the pressure or flow rate limit. If this condition is not satisfied, the feed flow rate in the standing wave equations (equations 1-6) is reduced until this condition is satisfied. In a like manner, one can start with a mobile phase velocity of a lesser percentage of the maximum flow rate limit, such as 50%, to arrive at the operating parameters.

Other variables can often be fixed at the outset to further minimize the number of variables that must be explored when optimizing the SMB system. For example, feed flow rate may be fixed because of the output requirements or raw material production constraints of the manufacturer. Similarly, in many instances the cost of the raw material will be so high, and the purity requirements so demanding (such as in pharmaceutical applications), that product purity and yield will essentially be dictated at the outset.

Optimal Column Configurations

The ability to allocate varying numbers of columns among zones, or to vary the length of the columns used in the SMB, for optimal efficiencies in systems with mass transfer effects is a particularly significant advantage of the present invention. Thus, as mentioned above, one can prescribe various column configurations (by varying column number and/or length), and determine the economic efficiency associated with each configuration using the design methods of this invention. One can use this process to optimize column configuration in binary systems as well as multicomponent systems.

Column allocation (zone lengths) is also critical to the satisfaction of demanding design criteria (such as purity and/or yield requirements), because under some circumstances one cannot even achieve a desired purity and yield unless zones are sufficiently long and/or columns are properly allocated. For example, if one assumes operation at the maximum zone flow rate (as constrained by the pressure or flow rate limit), one can readily estimate the operating parameters that satisfy the desired purity and yield requirements, using the standing wave equations of the present invention for different column configurations. One can then compare the various potential column configurations, and their economic efficiencies, to identify a system that most efficiently processes a given mixture. The equations of the present invention allow various column configurations to be scanned quickly and efficiently, without running time-consuming computer simulation programs.

One can engage in a similar iterative analysis to identify optimum column configurations when other operating parameters are prescribed, such as the feed rate. Additionally, when the number or length of columns available to a designer is not already fixed, one can improve upon this design process to test even more column configurations, and explore even more designs in an effort to optimize the system.

Thus, in one embodiment the invention provides SMBs for binary and multicomponent separations, in nonideal separations wherein linear isotherms are observed, in which column configuration is optimized for economic efficiency. In this embodiment the invention provides a method for chromatographically separating two or more components or fractions using a SMB, under linear isotherm conditions wherein non-negligible mass transfer resistances are observed, comprising:

a) providing a simulated moving bed that comprises a stationary phase, a first desorbent stream, and a first ring that comprises 4 zones and 5 or more columns, or 5 zones and 6 or more columns;

b) providing a feed stream that comprises a fast and a slow fraction and/or component;

c) introducing the desorbent stream and the feed stream to the SMB under conditions sufficient to separate the fast fraction or component from the slow fraction or component; and

d) withdrawing the fast fraction or component as a raffinate and the slow fraction or component as an extract from the SMB;

wherein the columns are allocated among the zones in a manner that optimizes economic efficiency for a sufficiently prescribed set of design and or operating parameters, as discussed more fully herein (including defined yields of the purified components and/or fractions, purity and yield of a desired component or fraction, defined maximum zone flow rates, and/or a defined feed flow rate), preferably for a desired yield and purity of the fast or slow component or fraction.

In preferred embodiments, the first ring comprises 4, 6, 8, 10, 12, 14, 16, 18, or 20 or more identically sized columns. In another preferred embodiment, economic efficiency is optimized by maximizing the throughput of the SMB, or by minimizing the desorbent use, for a desired yield and purity of the fast or slow fraction. In yet another embodiment the method is employed to resolve a multicomponent mixture, and the columns are similarly configured for optimum economics.

In another aspect the number of columns used in an SMB is optimized for a particular column allocation. Of course it will be understood in this embodiment that the number of columns for defined zone lengths can always be increased to improve the efficiency of the system. Therefore, in this context, an optimum design will provide greater than about 85%, 90%, 95%, 97%, 98%, or 99% of the theoretical throughput, or less than 125%, 110%, 105%, 103%, 102%, or 101% of the minimum desorbent consumption, each as defined by the standing wave design, at an infinite column number.

Exemplary Separations

As mentioned above, any chromatographic process can be used in the methods of the present invention, as long as linear isotherms are observed. Thus, the chromatographic method can be based upon differences in adsorption, partition, ion exchange, molecular exclusion, or affinity, within the linear isotherm regime. The method is generally applicable to multicomponent separations, and especially multicomponent separations in which the desired component exhibits an intermediate affinity for the selected adsorbent. However, as explained above, some of the methods can also be employed in binary systems (such as the method in which column configuration is optimized). Moreover, the method is also generally applicable to systems in which non-negligible mass transfer resistances are observed. However, as shown above, the methods of design and operation can also be applied to systems in which mass transfer resistances are not observed.

In a particularly preferred embodiment, however, the chromatographic process of the present invention is size exclusion chromatography (also known as gel permeation or gel filtration). In size exclusion chromatography, the process lacks any substantial attractive interaction between the stationary phase and component. The liquid or gaseous phase passes through a porous gel which separates the molecules according to size. The pores are normally small and exclude the larger component molecules, but allow smaller molecules to enter the gel, causing them to pass through a larger volume. This causes the larger molecules to pass through the column at a faster rate than the smaller ones. For the separation of biomolecules in aqueous systems, SEC is typically referred to as gel filtration chromatography (GFC), while the separation of organic polymers in non-aqueous systems is called gel permeation chromatography (GPC).

Examples of suitable gels include, among others, starch (including maize starch), crosslinked galactomannan, crosslinked dextran, agar or agarose, polyacylamides, copolymers of acylamide and methylene bis-acrylamide, copolymers of methylene bis-acrylamide with vinylethyl carbitol and with vinyl pyrrolidone, and the like. For more demanding environments, one should consider a rigid polymer-based gel made from a silica-based or polymer-based material. The preferred gels are crosslinked dextrans, such as the Sephadex series from Pharmacia Fine Chemicals, Inc., Piscataway, N.J.

Size exclusion methods can be used to purify various biological macromolecules including proteins and peptides, carbohydrates (i.e. polysaccharides), poly(nucleic acids) (including DNA and RNA fragments, and vaccines), lipids (including fatty acids, triacylglycerols, phospholipids, glycolipids, steroids, and terpenes), and blood plasma components. Size exclusion methods can also be used to separate various synthetic polymers based upon length, molecular weight, or other measure of size.

Proteins and peptides that can be purified using the methods of the present invention include insulin, human serum albumin, erythropoeitin, interleukin, interferon, human growth hormone, and bovine growth hormone. Generally speaking, the process can be used to purify any protein or peptide that comprises at least 2, 5, 10, or 25 amino acid (or synthetic amino acid) residues. The peptide or protein can be derived from natural sources, made using synthetic chemical techniques, or made from protein expression systems using recombinant DNA techniques. In one embodiment, the methods and processes of the invention are practiced using mixtures that do not contain insulin.

Similarly, the size exclusion processes can be used to separate carbohydrates greater than 3, 5, 10, or 20 saccharide units in length. The term carbohydrate generally refers to a compound of carbon, hydrogen, and oxygen that contains the saccharose unit or its first reaction product and in which the ratio of hydrogen to oxygen is the same as in water. Carbohydrates which can be separated by the present invention, however, be substituted or deoxygenated at one or more positions, in which case the ratio of hydrogen to oxygen will be different than water. Carbohydrates thus include substituted and unsubstituted oligosaccharides, and polysaccharides. The saccharide units can be an aldose or ketose, and may comprise 3, 4, 5, 6, or 7 carbons.

Size exclusion processes can also be used to separate synthetic polymers and copolymers based upon size or molecular weight. Exemplary polymers include polyolefins (such as polyethylene, poly(ethylene glycol), and polypropylene), polystyrene, poly(methyl methacrylate), and poly(vinyl alcohol). Generally, the polymer will comprise greater than 20, 50, or 100 monomeric units.

The method also has been found particularly useful in the purification of sugars from extraction media (especially acids) used in the sugar processing industry, using cation exchange resins such as the Dowex resins produced by Dow Chemical, made of sulfonated polystyrene. A preferred resin for separating glucose and xylose from sulfuric acid and acetic acid is Dowex 99, made from sulfonated polystyrene with approximately 6% divinylbenzene or a crosslinker. A preferred particle size is about 320 *u*m.

However, the process can be used generally to recover sugar from any acidic extraction medium, including acetic acid, citric acid, sulfuric acid, carbonic acid, hydrochloric acid, phosphoric, or sulfuric acid. Similarly, the invention can be used to purify any sugar, using a cation exchange resin under linear isotherms. As used herein "sugar" includes the monosaccharides glyceraldehyde, erythrose, threose, ribose, arabinose xylose, lyxose, allose, altrose, glucose, mannose, gulose, idose, talose, galactose, psicose, fructose, sorbose, tagatose, ribulose, xylulose, erythrulose, dihydroxyacetone, and oligosaccharides based thereon, including but not limited to sucrose, trehalose, maltose, cellobiose, gentiobiose, lactose, and raffinose.

Another preferred application of the methods of the present invention is in the purification of synthetic or naturally occurring pharmaceutical compounds. These compounds are particularly well suited for SMB purification because of their tremendous

expense, and the ability of SMB purifications to deliver higher yields than batch chromatography.

Linear separations are typically observed from this type system when the solubility of the components to be separated is low relative to the adsorbing capacity of the adsorbent. In a particularly preferred embodiment the SMBs are used to purify paclitaxel from a mixture of components such as cephalomannin, using a selective adsorbent (preferably a high capacity polystyrene divinyl-benzene adsorbent). A preferred solvent for such a system is ethanol, and its concentration preferably is between 30% and 100%.

In other embodiments, the SMBs are used in hydrophobic adsorption processes, or in ion exchange processes at low concentrations.

EXAMPLES

Example 1 -- Pilot Scale Purification of Insulin from Zinc Chloride/High Molecular Weight Protein Mixture

Materials: Insulin feed used in the single column and the SMB experiments was provided in a broth containing HMWP/HPI, insulin, $ZnCl_2$, and water. Glacial acetic acid was purchased from Mallinckrodt Baker Inc. (Paris, KY) and pure ethanol from Pharmaco Products Inc. (Brookfield, CT). Distilled deionized water (DDW) was obtained through a Milli-Q system by Millipore (Bedford, MA). HPLC-grade acetonitrile was purchased from Fisher Scientific (Fairlawn, NJ). Sulfate buffer was prepared from sodium sulfate and 85% phosphoric acid, which were purchased from Mallinckrodt Baker Inc. Sodium chloride and zinc chloride were also purchased from Mallinckrodt Baker Inc. Blue dextran used in bed porosity determination was purchased from Sigma Chemical Co. (St. Louis, MO). The gel particles have an average radius of 54 μm. All the columns and fittings were purchased from Ace Glass Inc. (Louisville, KY). The columns are 5.10 cm in diameter and 13.7 cm in packing length.

A Vydac C-18 HPLC column (25cm × 4.6 mm) for protein and peptide analysis was purchased from Vydac Co. (Hesperia, CA) and used to determine the concentration of BHI (Biosynthetic Human Insulin). A Waters insulin HMWP HPLC column (30cm × 7.8 mm) was purchased from Millipore Corp. (Milford, MA) and used to determine the concentration of HMWP.

Equipment: The HPLC system consists of two pumps (Waters 510), a tunable single-wavelength detector (Waters 486) and an injector (Waters U6K). A Pharmacia (Piscataway, NJ) fast protein liquid chromatography (FPLC) system was used in the single column experiments. This system consists of two pumps (Pharmacia P-500), a liquid chromatography controller (Pharmacia LCC-500), and an injection valve (Pharmacia MV-7). A lab-scale SMB unit was manufactured by Advanced Separation Technology (Lakeland, FL). It consists of a controller for the adjustment of the switching time and a frame that supports a rotation gear, a drive assembly, and a column rack. Two single-piston pumps (Model RHV) purchased from Fluid Metering Inc. (Syosset, NY) were used to control the flow rates for Zone II and Zone IV. The flow rates of the feed and desorbent were controlled by two FPLC pumps. The flow rates were reproducible and controlled to within ± 1%.

Column preparation: About 150 g of Sephadex G50 resin was slowly fed into a vessel containing 1.8 L of DDW. The vessel was rotated at 70 RPM for half an hour and then at 110 RPM for nine and a half hours to ensure complete mixing of the resin with DDW. DDW was decanted and 1N acetic acid was slowly added to the resin and agitated for 50 minutes. Then, the supernatant was decanted and the wet resin was transferred to a glass column, where it was washed with 1 N acetic acid. After repeating the washing step four times, the resin was slurried in 1 N acetic acid before column packing.

All columns were supplied by Ace Glass Company and designed to give 13.7cm packing height. Each column was connected with a column extender for packing convenience. The extended column was filled with 0.5 BV of 1N acetic acid. Resin slurry was poured into the column until it reached approximately 2/3 of the extended column. Excess liquid on the top of the resin packing was removed. At this point, the resin packing should be 0.8 cm higher than the target packing height and the weight of the packed column was measured in order to keep uniformity in the weight of each column. Note that the weight measured at this point is higher than the weight of final packed column, since the resin packing is higher than the target height. A solution of 20% ethanol was fed into the column until it filled 3/4 of the extended column. The dispersion was well mixed by shaking the column. The resin was then allowed to settle. When one inch of liquid head formed above the resin, the liquid was removed from the bottom of the column using a vacuum pump. Once most of the liquid was removed, the column was disconnected from the extender and attached to a pump (FPLC pump, Pharmacia) to continue the packing process.

A solution of 1N acetic acid was allowed to upflow through the column at a flow rate of 1mL/min for 50min. The flow rate was gradually increased every 15 minutes to the maximum flow rate (9 mL/min). After 30 minutes at the maximum flow rate, the direction of flow was changed to downflow. The flow rate was again increased in the same way as for upflow. At the maximum flow rate, downflow lasted for 50 minutes.

The HETP (Height Equivalent to Theoretical Plate) test was performed in order to check the column efficiency for each column. A 2-mL pulse of sodium chloride (5g/L in 1N acetic acid) was injected into the column, followed by elution with 1N acetic acid at the maximum flow rate. Since the conductivity detector has a relatively high flow resistance, the column effluent was split into two streams in a ratio of 8 to 1. The split is needed to keep the pressure drop in the column below 100 psi. The smaller stream was passed through the conductivity detector. Finally, the Number of Theoretical Plates (N) was determined from the conductivity peak with a target of greater than 150 plates.

***Single-Column Experiments*:** All experiments, including the SMB experiments were carried out at atmospheric pressure (1bar) and cold room temperature (4°C). The feed solution was equilibrated at 4 °C and used within 12 hours after the feed preparation. Before the experiments, the columns were equilibrated with 1 N acetic acid. Extra-column dead volume was determined by measuring dead volumes of the column cap and tubing separately. For the determination of dead volume of the column cap, the amount of water that filled in the cap was measured. Dead volume of the tubing was measured by a pulse test without the column after each single column experiment.

To perform pulse tests, a 2-mL loop was connected to the injection valve (Pharmacia MV-7). In the load position, the loop was filled with a feed solution. The eluent flow rate was controlled by a controller (Pharmacia LCC-500). Then the injection valve was switched to the inject position by the controller in order to start the injection. Data recording was started simultaneously. Three pulse tests were carried out: NaCl, $ZnCl_2$ and BHI. The concentrations of BHI were detected by the UV detector at 294 nm. All pulse tests were performed at a flow rate of 6 mL/min.

For frontal tests, 1 N acetic acid was used for column equilibration, followed by feeding the BHI solution into the column. After a concentration plateau appeared at the column outlet, 1 N acetic acid was used to wash the column. Because of the high BHI concentration, the effluent was monitored at the wavelength of 306 nm. Three frontal tests were carried out, each at different flow rates, 2.0 mL/min, 4.0 mL/min, and 8.1 mL/min.

For multiple frontal tests, both FPLC pumps were used. One pump delivered 1N acetic acid and the other BHI solution. The two streams were mixed before entering the column. The total flow rate for the mixed stream was kept constant at 6 mL/min. Various BHI compositions (20%, 40%, 60%, 80% and 100%) were obtained by changing the ratio of the two streams. The ratio was changed only after a concentration plateau appeared at the column outlet. The column effluent was monitored at 310 nm using a UV detector.

SMB experiments: The 10 columns in the SMB were packed with Sephadex G50 resin using the aforementioned method. The column configuration was either 2-3-3-2 (there were 2, 3, 3, and 2 columns in Zones I, II, III, and IV, respectively) or 2-2-4-2. The extra-column dead volume was determined by measuring the amount of water that filled in the tubing and rotary valve. Before each SMB experiment, the flow rates of the four pumps were set manually and were checked later periodically during the experiment to ensure accuracy. The switching time was set using the SMB controller. The experiment was started by turning on the pumps simultaneously. Feed and desorbent were continuously pumped into the columns. The feed for Ring I was prepared by dissolving crude insulin powder (containing $ZnCl_2$) in an HMWP broth. The feed for Ring II was a binary mixture of BHI and $ZnCl_2$, which was made by dissolving the crude insulin powder in 1 N acetic acid. The desorbent was 1 N acetic acid. Samples were collected from the extract port and the raffinate port over an entire switching period (between two switches). Therefore, the concentration of each sample represents the average concentration over a switching period. The Ring I experiments were stopped in the middle of the 45^{th} step and the Ring II experiment was stopped in the middle of the 61^{st} step. Zone profiles were then obtained by collecting samples at the sampling ports, which were located at each column outlet.

Column characterization: The results of column characterization are listed in Table 4. The Number of Theoretical Plates (N) of all columns estimated from the NaCl pulse tests were found to be greater than 150 plates.

Table 4. Summary of the Results of Column Characterization

Column name	Weight* (g)	Retention time of NaCl (min)	N (plates)
Column A	308.3	28.85	371
Column B	313.2	28.91	691
Column C	314.1	28.93	606
Column D	310.2	28.90	518

Column E	308.0	28.88	563
Column F	308.6	28.82	416
Column G	309.7	28.89	670
Column H	309.2	28.88	670
Column I	307.5	28.83	478
Column J	310.4	28.89	500
Average	309.9	28.88	
Max. Deviation	1.3 %	0.21%	

*The weight refers to the packing weight for an intermediate packing volume of 304 mL, which is larger than the final bed volume (280 mL).

Pulse tests: The chromatograms of the pulse tests are shown in Figure 9. The elution volume of each pulse is estimated from the mass center of the chromatogram and is used to determine the column properties and size exclusion factors. Note that the extra-column dead volume is subtracted to obtain the net elution volume through the column.

The elution volume of a blue dextran pulse is the inter-particle volume or void volume (V_0), because the blue dextran molecule is much larger than the average resin pore size and is totally excluded from the particle. The bed voidage, ε_b, is calculated from the void volume as follows:

$$\varepsilon_b = \frac{V_0}{BV} \tag{36}$$

where BV is the bed volume (mL).

The NaCl molecule is smaller than the molecule of HPI, BHI, or $ZnCl_2$, and is chosen as the tracer to estimate intra-particle volume. The total void volume (V_t) including inter-particle and intra-particle volume is obtained from the NaCl pulse. Combined with the void volume, the total void volume can be used to calculate the particle porosity, ε_p.

$$\varepsilon_p = \frac{V_t - V_0}{BV - V_0} \tag{37}$$

With the bed voidage (ε_b) and the particle porosity (ε_p), the size exclusion factors of BHI and $ZnCl_2$ can be estimated as follows:

$$Ke = \frac{\frac{V_e}{BV} - \varepsilon_b}{(1-\varepsilon_b)\varepsilon_p} \tag{38}$$

where Ke is the size exclusion factor and V_e is the elution volume of BHI or $ZnCl_2$. The values of ε_b, ε_p, the extra-column dead volume, and Ke are listed in Table 5.

Table 5. Summary of the Results of the Pulse Tests in the Lab and Plant Scale Columns

	ε_b	ε_p	Ke of BHI*	Ke of $ZnCl_2$	Extra-column dead volume	Single bed volume
Lab-scale	0.35	0.89	0.68	0.99	11.1 mL	280 mL
Plant-scale	0.35	0.89	0.74	0.99		

*The Ke estimated from the lab-scale column with a small pulse, in which the peak concentration is very low, is close to intrinsic Ke. The Ke for the plant-scale column is an apparent Ke, which is concentration-dependent.

The estimated column properties and size exclusion factors for the lab-scale columns (Table 5) were applied to a detailed rate model, VERSE, to simulate the data of the lab-scale experiments. The mass-transfer and numerical parameters used in the simulations are listed in Table 6. The simulated chromatograms are in good agreement with the experimental data as shown in Figure 9.

Saturation and elution tests: During the pulse test of BHI, the injected BHI solution is diluted by more than 25- fold because the feed volume is only 2 mL (0.7% bed volume). The dilution in SMB, however, is usually much less than the associated batch chromatography process. In addition, the operation of SMB is similar to a long pulse, i.e. a large amount of loading followed by elution. For these reasons, long pulse tests including saturation with BHI solution and elution with 1 N acetic acid were conducted.

Table 6. Mass Transfer and Numerical Parameters Used in the Simulations of This Study

	Mass transfer parameters			
	Blue dextran*	NaCl*	BHI**	$ZnCl_2$**
D_∞ (cm^2/min)	2.21×10^{-5}	4.88×10^{-4}	5.49×10^{-5}	3.96×10^{-4}
D_p (cm^2/min)	-	3.53×10^{-4}	2.29×10^{-5}	1.65×10^{-4}
K_f (cm/min)	The Wilson and Geankoplis correlation (1966)			
E_b (cm^2/min)	The Chung and Wen correlation (1968)			

Numerical parameters				
Axial elements per column	Collocation points		Absolute tolerance	Relative tolerance
	Axial	Particle		
50	4	2	0.0001	0.001

* D_∞'s of blue dextran and NaCl are obtained from Hritzko et al. (1999) and adjusted with temperature and viscosity using the Wilke and Chang (1955) correlation. D_p of NaCl is estimated from the Mackie and Meares correlation (1955).

** D_∞'s and of BHI and $ZnCl_2$ are obtained from the Wilke and Chang (1955) correlation. D_p's of BHI and $ZnCl_2$ are obtained by fitting the data with VERSE simulations.

Figure 10 shows the chromatograms of the saturation and elution tests at three different flow rates and the results of the simulations (dashed lines) with the intrinsic *Ke* estimated from the small pulse test (Table 5). The simulated chromatograms are ahead of the data for both loading and elution processes at all three flow rates.

***Multiple frontal test*:** A multiple frontal test was first conducted without the column. This test is to determine the extra-column dead volume and to obtain the calibration curve of UV absorbance as a function of concentration. The chromatogram shown in Figure 11a is used to estimate the dead volume present in the mixer and the connecting tubing. The dead time of each frontal obtained without the column is subtracted from the breakthrough time of the corresponding frontal obtained with the column. The chromatogram of the multiple frontal test with the column is shown in Figure 11b.

Following the procedure described by Ma et al. (1996), one can calculate the amount of adsorbed BHI on the resin associated with each plateau concentration. The isotherm adsorption data are shown in Figure 11c. An anti-Langmuir isotherm model was applied to fit the data.

The anti-Langmuir isotherm parameters were used in a simulation to predict the multiple frontal test data. Good agreement between the model prediction and data is shown in Figure 11b. Since the curvature of the isotherm is quite small, the isotherm can be well represented by a linear adsorption isotherm or an apparent *Ke*, which has a higher value than the intrinsic *Ke*. For this reason, the multiple frontal test data can be simulated with an apparent *Ke*. The simulated chromatograms with adsorption (anti-Langmuir) and with the apparent *Ke* are almost identical (Figure 11b). The value of the apparent *Ke* applied in the simulations is 0.74 (>0.68, the value of the intrinsic *Ke* of BHI).

With the isotherm parameters and the apparent *Ke* of BHI, one can rerun the simulations for the saturation and elution processes (the long pulse). The simulated chromatograms with adsorption and with the apparent *Ke* are closer to the experimental data than the simulations with the intrinsic *Ke* (Figure 10). The experimental frontal waves still lag behind the model prediction because of the excessive adsorption during the initial loading period. The disagreement, however, does not have a negative impact on the design of SMB, because the predicted adsorption wave is ahead of the experimental data.

***SMB experiments*:** The extra-column dead volume in the SMB unit was estimated to be 10.4 mL per column or 3.7% of the bed volume. This dead volume was taken into consideration in designing the zone flow rates and switching time of the SMB process. The design results are summarized in Table 7.

The maximum interstitial velocity for the Sephadex G50 resin cannot exceed 1.28 cm/min. For the lab-scale columns (5.1 cm in diameter), the maximum zone flow rate is estimated to be 9 mL/min. This flow rate limit was applied in the design of both Ring I and Ring II with the lab-scale columns. Since the same size columns were used in both Ring I and Ring II experiments, the extract flow rate of Ring I is not matched by the feed flow rate of Ring II as shown in Table 7. This mismatch, which is considered in calculating the overall throughput, however, does not affect the validation of the tandem SMB design and the model.

The SMB experiment Run 1 (Ring I) lasted for 21 hours or 45 cycles. The simulation and experimental data of the effluent histories at the raffinate and extract ports and the mid-cycle column profiles at the final cycle are shown in Figure 12. Close agreement between the model prediction and the experimental data indicates that the column properties and size exclusion factors used in the SMB designs are accurate and the design method is robust, even though the simulations do not accurately predict the data of the batch frontal processes.

Table 7. Operating Conditions Designed to Test the Tandem SMB Process*

		Ring I		Ring II
		Run 1	Run 2	Run 3
Zone configuration		2-3-3-2	2-2-4-2	2-3-3-2
Zone flow rates (mL/min)	Zone I	8.31	8.48	8.01
	Zone II	5.01	5.13	6.85

	Zone III	8.06	7.38	7.95
	Zone IV	4.92	5.03	6.66
Inlet and outlet flow rates (mL/min)	Feed	3.05	2.25	1.10
	Desorbent	3.39	3.46	1.35
	Raffinate	3.13	2.36	1.29
	Extract	3.30	3.35	1.17
Switching time (min)		28.0	27.4	33.7

* The *Ke* of BHI used in the design is apparent *Ke* (= 0.74) and the extra-column dead volume per column is 10.4 mL per column or 3.7% of the bed volume.

Among the SMB Run 1 experimental results, the column profile of BHI (Figure 12c) is the most interesting. In Ring I, slight fronting of BHI is observed in Figure 12c. As a result, a small amount of BHI is lost in the raffinate as shown in Figure 12a. The loss of BHI, however, is only 3% (Table 8), which is much less than that of the reference batch SEC process (11%). The improvement of the yield by SMB Ring I over the reference batch SEC process is attributed to the separation characteristics of SMB, i.e. only partial separation is needed in SMB. The overlapping band remains in the SMB columns. By contrast, the overlapping band is recycled in the batch process.

Table 8. Summary of the Experimental Results of SMB

		Run 1 (Ring I)	Run 2 (Ring I)	Run 3 (Ring II)
Impurity in product	HMWP/HPI (ppm)	0	0	0
	$ZnCl_2$ (g/g BHI)	—	—	4×10^{-6}
Purity (%)*		100	100	100
Yield (%)**		97.0	99.3	> 96.7 (99.7)†
Throughput (L/hr/100L BV)		6.54	4.82	2.36
Solvent consumption (L/Kg BHI)		32.2	18.5	18.3
Overall yield (%)			> 96.0 (99.0) †	
Overall throughput (L/hr/100L BV)			1.19	
Overall solvent consumption (L/Kg BHI)			42.0	

* The purity in Ring I is defined as $(C_{BHI} + C_{ZnCl2})/(C_{BHI} + C_{ZnCl2} + C_{HMWP}) \times 100\%$.

** The yield was estimated with the concentration averaged over one switching period of the final cycle.

† The Ring II experiment (Run 3) did not reach the cyclic steady state. The values in the parentheses were estimated from the simulations at cyclic steady state.

The fronting of BHI in Zone III of Ring I can be simulated by using a larger axial dispersion coefficient (E_b). The results of the simulations with different E_b's for BHI in Zone III are plotted in Figure 13. As the E_b increases, the loss of BHI in the raffinate increases (Figure 13a) and the adsorption wave of BHI in Zone III spreads out (Figure 13c). Figure 13 shows that the breakthrough curve of BHI in the raffinate can be well predicted when E_b value is 40 times as large as that estimated from the Chung and Wen correlation (1968). To reduce the loss of BHI in Ring I, the fronting should be considered and the fitted E_b value should be used in the standing wave design.

Table 9 shows the results of Ring I design, in which the fronting of BHI is considered by using the fitted E_b (40 times as large as that estimated from the Chung and Wen correlation). Different zone configuration was investigated in the standing wave design. To reduce the difference between the true moving bed and the simulated moving bed, at least 2 columns are needed for each zone. For some zone configurations, there are no feasible operating conditions that can meet the yield requirement (99.99% for BHI). Among the three zone configurations that can meet the high yield requirement, 2-2-4-2 gives the lowest solvent consumption (desorbent to feed ratio) as shown in Table 9. To verify the design results, VERSE simulations were conducted. The simulation results are listed in Table 10.

The zone configuration of 2-2-4-2 and the associated operating parameters listed in Table 9 was then applied in the SMB experiment Run 2. The experimental data and simulation results are shown in Figure 14. Compared with Figure 12a, Figure 14a shows that the loss of BHI in the raffinate is significantly reduced. As a result, the yield of BHI increases from 97.0% in Run 1 to 99.3% in Run 2 (Table 8). The fronting of BHI in Zone III is well predicted and the adsorption wave of BHI is confined within Zone III as shown in Figure 14c. This result indicates that a well-designed SMB is able to overcome the BHI fronting. Furthermore, the close agreement between the data and model prediction proves

that the model-based design approach including standing wave design and the VERSE simulation is efficient.

Table 9. Standing Wave Design Results for Ring I with BHI E_b in Zone III = 40 C&W*

Zone configuration	Zone flow rate (mL/min)				Switching time (min)	Desorbent / Feed
	I	II	III	IV		
4-2-2-2	Not feasible for the desired purity and yield					
2-4-2-2	Not feasible for the desired purity and yield					
2-2-4-2	8.48	5.13	7.38	5.03	27.4	1.54
2-2-2-4	Not feasible for the desired purity and yield					
3-3-2-2	Not feasible for the desired purity and yield					
3-2-3-2	8.48	5.17	7.17	5.05	27.2	1.72
3-2-2-3	Not feasible for the desired purity and yield					
2-3-3-2	Not feasible for the desired purity and yield					
2-3-2-3	Not feasible for the desired purity and yield					
2-2-3-3	8.47	5.13	7.12	5.04	27.4	1.73

*C&W stands for the value estimated from the Chung and Wen correlation. Zone flow rates are less than 8.5 mL/min, which is 5% lower than the theoretical maximum value.

Table 10. Summary of Simulation Results of Ring I with BHI E_b in Zone III = 40 C&W

Zone configuration	Concentration in extract*			Yield (%)	Mass balance (%)**
	$C_{BHI}/C_{F,BHI}$	$C_{HMWP}/C_{F,HMWP}$	C_{HMWP}/C_{BHI} (mg/kg)		
2-2-3-3	0.592	1.91×10^{-4}	1.09	99.7	99.7
2-2-4-2	0.668	3.29×10^{-4}	1.66	99.4	99.4
3-2-3-2	0.597	12.7×10^{-4}	7.18	99.1	99.1

* The subscript "F" represents feed.
** Simulation finished at the end of 50th cycle.

The Ring II SMB experiment (Run 3) was carried out after the Ring I SMB experiments. The operating conditions of Ring II are listed in Table 7. The experimental results of Ring II are summarized in Table 8 and effluent histories and column profiles are plotted in Figure 15. The model predication is verified again with the experimental data (Figure 15). Note that the Ring II experiment (Run 3) did not reach cyclic steady state and the BHI concentration at the final step (the 61st step) was used to calculate the yield. Since the model is verified with the transient data, the model predicted concentration at cyclic steady state (after 150 steps) can be used to estimate the actual yield. The estimated yield is listed in the parentheses in Table 8. The BHI concentration at cyclic steady state is higher than that at transient state. For this reason, the yield at cyclic state is higher than that at the 61st step.

The overall yield, throughput, and solvent consumption of the Ring I and Ring II SMB experiments (Run 2 and Run 3) were calculated. The overall yield is the product of the yields of SMB Run 2 and Run 3.

Since the extract flow rate of Ring I is higher than the feed flow rate of Ring II, more resin are needed in Ring II than in Ring I such that Ring I and Ring II can be operated in tandem. This can be done by increasing the diameters of the columns in Ring II while keeping the interstitial velocities the same as those in the Ring II experiment. For this reason, the overall throughput (per 100 L bed volume) of the tandem SMB experiments was calculated as follows:

$$\frac{F_F}{\left(1+\frac{F_E^{\text{Ring I}}}{F_F^{\text{Ring II}}}\right)\times(10BV)}\times(60\,\text{min/hr}\times 100\,\text{L}) \qquad (39)$$

where F_F is the feed flow rate (mL/min), F_E is the extract flow rate (mL/min), BV stands for the bed volume (mL) of a single column in the experiments.

For the similar reason, the different bed volumes for Ring I and Ring II in the tandem SMB should be considered in estimation of the overall solvent consumption. In addition, the feed concentration of Ring II (SMB Run 3) is not the same as the extract concentration (or product concentration) of Ring I (SMB Run 2) as shown in Table 8. In the actual tandem SMB, these two concentrations should be the same. To estimate the final product concentration of the tandem SMB from the individual Ring I and Ring II experiments, the concentration ratio of the extract of Ring I to the feed of Ring II should be

used. The estimated final product (BHI in the raffinate of Ring II) concentration is applied to calculate the overall solvent consumption as follows:

$$\frac{F_D^{\text{Ring I}} + \frac{F_E^{\text{Ring I}}}{F_F^{\text{Ring II}}} F_D^{\text{Ring II}}}{\left(\frac{F_E^{\text{Ring I}}}{F_F^{\text{Ring II}}} F_R^{\text{Ring II}}\right)\left(\frac{C_{BHI,Ext}^{\text{Ring I}}}{C_{BHI,Feed}^{\text{Ring II}}} C_{BHI,Raff}^{\text{RingII}}\right)} \times (1000\,\text{mL/L}) \qquad (40)$$

where F_D is the desorbent flow rate (mL/min), F_R is the raffinate flow rate (mL/min), and subscript "Ext" stands for extract and "Raff" for raffinate. The unit of the BHI concentration is g/L.

The calculated results are summarized in Table 8. Since the Ring II experiment (Run 3) did not reach cyclic steady state, the calculated yield based on the last data point in the effluent history curve is lower than the yield at cyclic steady state. On the basis of the VERSE simulation at cyclic steady state for Ring II, the projected yield for Ring II is 99.7%. In other words, if the Ring II experiment is run long enough to reach cyclic steady state (after 150 steps), the tandem SMB process will have an overall yield of 99%. The overall throughput of the SMB process is 1.19 L/hr/100L BV. All these experimental results show that the SMB process is more efficient than the current batch process for BHI purification. If the maximum allowable flow rate were not as constrained by the resin, then one could expect even greater improvements over the yield and throughput from batch systems.

Example 2 -- Purification of Sugars from Sugar/Acetic Acid/Sulfuric Acid Mixture

***Parameter validation*:** Column profile data are collected from a preliminary four-zone simulated moving bed experiment for the purification of glucose and xylose from acetic acid and sulfuric acid, and compared to simulation results in order to validate the isotherm and mass-transfer parameters as well as the port-switching in the model. Two sets of pulse data were analyzed to insure the accuracy and applicability of the mathematical model. These data sets were previously published by Wooley et al. (1998).

The first set of pulse data is made up of single-component pulse injections to a packed column (Figure 16). Wooley et al. (1998) reported the first moments for pulses of the four solutes in this system. The partition coefficients are calculated from the first moments of these pulses, according to the following material balance:

$$a_i = \frac{F(t_{ri} - t_{0i} - t_p/2)}{V_c(1-\varepsilon_b)(1-\varepsilon_p)} \quad (56)$$

where a_i is the partition coefficient in ml/ml solid volume (S.V.), F is the volumetric flow rate of the feed, t_{ri} is the solute retention time (first moment), and t_p is the time of the pulse injection. The term t_{0i} is the touring time of solute i (neglecting adsorption), and it is calculated as

$$t_{0i} = \frac{V_c[\varepsilon_b + (1-\varepsilon_b)Ke_i\,\varepsilon_p]}{F} \quad (57)$$

Table 11 lists the partition coefficients for the four components in this system. Solid lines in Figure 16 represent simulation results. Literature values of the Brownian diffusivity can be found for sulfuric acid (Cussler, 1984), glucose (Doran, 1995), xylose (Lielmezs et al., 1990), and acetic acid (Cussler, 1984). The axial dispersion coefficient is calculated from the empirical correlation $E_{bi}^{m} = 0.05u_0^{m}$ (Wooley et al., 1998). The film mass-transfer coefficient, k_f, is calculated from the Wilson and Geankoplis (1966) correlation, and the intraparticle diffusivity, D_p, is computed from equation 23, based on the values of the lumped mass-transfer parameter (K_f) reported by Wooley et al. (1998). Mass-transfer parameters for Figure 16 are listed in Table 12. The data at 10 ml/min (Figure 16) are well predicted by the model. To validate the parameters, another set of single-column pulse data were compared to simulations. Figure 17 shows pulse data at a feed flow rate of 80 ml/min.

Standing wave designs: To compare designs for different column configurations and different splitting strategies, it is necessary to define a set of standard operating parameters. In each of the separation strategies shown in this section, two 20-column SMB systems in series are used to purify the center cut (which in this case consists of the two sugars glucose and xylose). For each case, the feed to the first SMB has a flow rate of 33.3 ml/min and a composition given in Table 13. The feed flow rate to the second SMB is taken as the flow rate of that product from the first SMB (raffinate or extract) that contains the unresolved components. In the simulations, the feed to the second SMB in each pathway is taken as the time-averaged composition at steady state; in reality, the concentration of each component changes with time even when the system has reached a cyclic steady-state. The yield is set to 0.90 for each component at each SMB step for the cases in which complete resolution of all components is desired; the yield is set to 0.50 for components that are allowed to distribute among the two product ports. The yield of 0.90 is

approximately the value that was obtained from the SMB experiment for parameter validation (Figure 18).

Figures 19 and 21 show column profiles for two strategies for isolating glucose and xylose from a feed mixture that contains both sulfuric acid and acetic acid, via complete separation of the two sugars from one of the acids in each step. The numerical parameters used in the simulations are listed in Table 14. The operating parameters and product compositions are listed in Table 15. The column configuration for each ring in each strategy is determined by doing a computer search of the standing wave designs of all possible configurations that satisfy the desired purity and yield, and selecting the configuration for which the standing wave design requires the lowest desorbent consumption. The column profiles are taken after 400 switch times; at this point, the concentration of each component has nearly approached a limiting value. The mass-balance is checked for each component over one switch interval; for each component, if the difference between the mass introduced during the switch interval and the mass leaving the system through the two product ports is less than 0.1%, then the system is defined here to be at cyclic steady-state. (This same criterion is used in the subsequent experiments.)

Figures 21 and 23 show column profiles for two strategies for isolating the two sugars via complete separation from one acid and partial separation from the other in the first step and complete separation from the other acid in the second step. The operating parameters and product compositions are listed in Table 16.

One can see from Table 17 that the total desorbent consumption (D_{total}/F) is much lower for the cases in which one component is allowed to distribute (3.27 and 3.24 for Figures. 22 and 23, respectively) compared to those in which complete separation is required (6.82 and 5.83 for Figures 19 and 21, respectively). Also, performing the easier separation first in the complete-separation case uses 17% less desorbent (Table 17). The two strategies explored for the cases in which one component is allowed to distribute among the two product ports yield almost the same desorbent usage (Table 17).

Comparison between mass-balances and detailed rate model simulations: Tables 16 and 17 show the comparison between the mass-balance estimates of product concentrations and the concentrations obtained after detailed simulations based on the given operating conditions. One can see that the mass-balance approach is generally conservative in that the desired product concentrations are underestimated by 3 to 15% while the impurity concentrations are overestimated up to fifty fold. It should be noted in Figures. 20

to 21 that within a given zone some waves are not standing but are traveling either faster or slower than the selected standing wave. For example, in Figure 19, the adsorption waves of xylose and acetic acid downstream from the feed port do not migrate as far through that zone as glucose (which is the standing wave there). Xylose and acetic acid are effectively "pinched" toward the feed port because the migration velocity of these solutes is relatively slow in this zone.

Table 11. Isotherm Parameters Based on the Pulse Profiles from Figure 16

Component, i	K_{ei}	t_{ri} [min]	t_{0i} [min]	a_i [ml/ml S.V.]
Sulfuric acid	0.244	13.6	12.6	0.000
Glucose	0.417	19.3	14.5	0.555
Xylose	0.417	19.9	14.5	0.639
Acetic acid	0.417	26.1	14.5	1.54

Table 12. Mass-Transfer Parameters Used in the Simulation of the Pulse Experiments in Figure 16

Component, i	D_i^{∞} [cm^2/min]	E_{bi} [cm^2/ min]	k_{fi} [cm/min]	K_{fi} [1/min]	D_{pi} [cm^2/min]
Sulfuric acid	2.42×10^{-3}	0.282	0.698	1.5	1.8×10^{-4}
Glucose	1.08×10^{-3}	0.282	0.519	3.0	2.3×10^{-4}
Xylose	1.04×10^{-3}	0.282	0.398	3.5	2.7×10^{-4}
Acetic acid	1.69×10^{-3}	0.282	0.550	10.5	1.0×10^{-4}

Table 13. System and Operating Parameters for the SMB Experiment in Figure 18

Parameter	Value
Number of columns	20
Column length	100.0 cm
Column inner diameter	3.37 cm
Packing porosity, ε_b	0.39
Particle porosity, ε_p	0.60

Column configuration*	3—4—9—4
Switching time	3.0 min
Feed flow rate	33.3 ml/min
Desorbent flow rate	110.0 ml/min
Raffinate flow rate	112.0 ml/min
Extract flow rate	21.3 ml/min
Zone I flow rate	206.0 ml/min
Zone II flow rate	174.7 ml/min
Zone III flow rate	208.0 ml/min
Zone IV flow rate	96.0 ml/min
Sulfuric acid feed concentration	11.3 mg/ml
Glucose feed concentration	9.58 mg/ml
Xylose feed concentration	40.7 mg/ml
Acetic acid feed concentration	16.8 mg/ml

* Allocation of columns in zones I, II, III, and IV, respectively.

Table 14. Numerical Parameters Used in the Simulations

Parameter	Single-Column	SMB
Number of axial elements	400	1000
Number of collocation points per element	4	4
Number of collocation points per particle	4	2
Absolute tolerance on concentration	0.001 mg/ml	0.01 mg/ml
Relative tolerance on concentration	0.0001	0.001
Maximum step time in integration	0.1 bed volumes	0.1 bed volumes

Table 15. Operating Parameters and System Output for the SMB Processes That Give Complete Separation of All Three Groups of Components

Parameter	Figure 19a (Ring A)	Figure 19b (Ring B)	Figure 20a (Ring A)	Figure 20b (Ring B)
Configure	4—6—6—4	4—6—6—4	5—5—8—2	5—5—7—3
$\Delta\delta$	0.326	0.359	0.359	0.326
t_s [min]	4.79	1.91	5.35	2.06

F [ml/min]	33.3	83.1	33.3	72.4
D [ml/min]	86.9	139.6	78.3	115.2
R [ml/min]	37.1	114.9	72.4	85.8
E [ml/min]	83.1	107.8	39.2	101.8
F^{I} [ml/min]	174.1	441.9	156.9	314.7
F^{II} [ml/min]	90.9	334.1	117.6	212.9
F^{III} [ml/min]	124.2	417.2	150.9	285.3
F^{IV} [ml/min]	87.2	302.3	78.5	199.5
β^{I}	(2.08)	(2.64)	(3.50)	(2.48)
β^{II}	(2.91)	(1.99)	(1.07)	(2.26)
β^{III}	(1.78)	(2.35)	(2.88)	(2.16)
β^{IV}	(2.31)	(1.75)	(0.89)	(1.91)
Y_1^R	0.99 (0.90)	0.74 (0.90)	0.99 (0.90)	0.98 (0.90)
Y_2^R	0.07 (0.10)	0.98 (0.90)	1.00 (0.90)	0.02 (0.10)
Y_3^R	0.04 (0.10)	0.99 (0.90)	1.00 (0.90)	0.01 (0.10)
Y_4^R	0.00 (0.10)	0.04 (0.10)	0.03 (0.10)	0.25 (0.10)
Y_1^E	0.01 (0.10)	0.26 (0.10)	0.01 (0.10)	0.02 (0.10)
Y_2^E	0.93 (0.90)	0.02 (0.10)	0.00 (0.10)	0.95 (0.90)
Y_3^E	0.96 (0.90)	0.01 (0.10)	0.01 (0.10)	0.97 (0.90)
Y_4^E	1.00 (0.90)	0.96 (0.90)	0.97 (0.90)	0.75 (0.90)
C_1^R [mg/ml]	10.07 (9.15)	0.04 (0.04)	5.14 (4.68)	4.26 (3.90)
C_2^R [mg/ml]	0.17 (0.86)	2.54 (2.33)	4.57 (3.96)	0.08 (0.39)
C_3^R [mg/ml]	0.07 (3.66)	11.22 (10.17)	19.29 (16.85)	0.24 (1.63)
C_4^R [mg/ml]	0.05 (1.51)	0.08 (0.50)	0.07 (0.77)	0.13 (0.01)
C_1^E [mg/ml]	0.07 (0.45)	0.01 (0.01)	0.11 (0.96)	0.08 (0.37)
C_2^E [mg/ml]	3.57 (3.45)	0.07 (0.28)	0.02 (0.81)	3.08 (2.92)
C_3^E [mg/ml]	15.62 (14.67)	0.28 (1.20)	0.57 (3.46)	13.35 (12.34)
C_4^E [mg/ml]	6.94 (6.04)	5.16 (4.82)	13.82 (12.80)	0.03 (0.04)

For all cases, $\varepsilon_b = 0.39$, $\varepsilon_p = 0.60$, $L_c = 100.0$ cm. System output values are from VERSE simulations. Values shown in parentheses represent mass-balance approximations.

Table 16. Operating Parameters and System Output for the SMB Processes in Which One Component Is Allowed to Distribute Between Two Product Ports

Parameter	Figure 21a (Ring A)	Figure 21b (Ring B)	Figure 22a (Ring A)	Figure 22b (Ring B)
Configure	5—5—6—4	5—5—6—4	3—7—3—7	5—5—6—4
$\Delta\delta$	0.326	0.359	0.359	0.326
t_s [min]	4.75	3.93	4.91	3.83
F [ml/min]	33.3	42.8	33.3	40.7
D [ml/min]	46.2	62.6	50.5	57.9
R [ml/min]	36.7	54.9	40.7	45.3
E [ml/min]	42.8	50.5	43.1	53.3
F^{I} [ml/min]	134.5	212.4	172.0	167.1
F^{II} [ml/min]	91.7	161.9	129.0	113.8
F^{III} [ml/min]	125.0	204.7	162.3	154.5
F^{IV} [ml/min]	88.3	149.8	121.6	109.2
β^{I}	(2.46)	(2.63)	(2.49)	(2.46)
β^{II}	(2.27)	(1.99)	(2.16)	(2.27)
β^{III}	(2.15)	(2.35)	(2.23)	(2.15)
β^{IV}	(1.93)	(1.76)	(1.91)	(1.94)
Y_1^R	0.99 (0.90)	0.75 (0.90)	0.70 (0.50)	0.98 (0.90)
Y_2^R	0.04 (0.10)	0.98 (0.90)	0.05 (0.10)	0.02 (0.10)
Y_3^R	0.02 (0.10)	0.99 (0.90)	0.02 (0.10)	0.01 (0.10)
Y_4^R	0.27 (0.50)	0.02 (0.10)	0.03 (0.10)	0.27 (0.10)
Y_1^E	0.01 (0.10)	0.25 (0.10)	0.30 (0.50)	0.02 (0.10)
Y_2^E	0.96 (0.90)	0.02 (0.10)	0.95 (0.90)	0.95 (0.90)
Y_3^E	0.98 (0.90)	0.02 (0.10)	0.98 (0.90)	0.98 (0.90)
Y_4^E	0.73 (0.50)	0.97 (0.90)	0.96 (0.90)	0.73 (0.90)
C_1^R [mg/ml]	10.19 (0.25)	0.10 (0.13)	6.46 (4.63)	5.68 (5.23)
C_2^R [mg/ml]	0.15 (0.87)	5.47 (5.02)	7.75 (7.05)	0.16 (0.70)
C_3^R [mg/ml]	0.48 (3.70)	24.08 (21.80)	33.57 (29.97)	0.40 (3.02)
C_4^R [mg/ml]	4.10 (7.61)	0.15 (0.74)	0.43 (1.37)	0.10 (0.19)
C_1^E [mg/ml]	0.18 (0.88)	0.04 (0.02)	2.64 (4.38)	0.10 (0.49)
C_2^E [mg/ml]	7.16 (6.70)	0.14 (0.61)	0.06 (0.74)	5.62 (5.32)
C_3^E [mg/ml]	31.08 (28.48)	0.54 (2.64)	0.22 (3.15)	25.02 (23.05)

C_4^E [mg/ml]	9.56 (6.51)	7.86 (7.30)	12.43 (11.66)	0.24 (0.16)

For all cases, $\varepsilon_b = 0.39$, $\varepsilon_p = 0.60$, $L_c = 100.0$ cm. System output values are from VERSE simulations. Values shown in parentheses represent mass-balance approximations.

Table 17. Comparison of Splitting Strategies

	Without Resistance		With Resistance	
Strategy	D_{total}/F	$C_{glu,prod}/C_{glu,feed}$	D_{total}/F	$C_{glu,prod}/C_{glu,feed}$
(a) Figure 8	4.62	0.415	6.82	0.265
(b) Figure 9	4.20	0.453	5.83	0.322
(c) Figure 10	2.30	0.830	3.27	0.571
(d) Figure 11	2.30	0.830	3.24	0.587

Figure 7 illustrates the strategies without mass-transfer resistance, while Figures 20 to 24 illustrate the strategies with mass-transfer resistance. In each case, the feed flow rate to the first SMB is 33.3 ml/min.

Example 3 -- VERSE Rate model

To check the validity of the design method derived from the standing wave analysis, several simulations have been run in these Examples. For single-column and multiple-column studies, a mathematical model based on pore diffusion has been used. The numerical solutions of the governing equations and their boundary conditions as well as the numerical methods used to solve them have been reported previously (Berninger et al., 1991; Ma et al., 1996; Whitley, 1990) as the VERSE model. The equations are solved by the method of orthogonal collocation on finite elements in the spatial direction, and DASSL (Petzold, 1982) is used to integrate in the time domain. The model assumes uniform spherical adsorbent particles, plug flow with constant linear velocity, local equilibrium within the adsorbent and constant diffusivities.

Example 4 -- Determination of Decay Coefficients

To make a design in the presence of mass-transfer resistance (equations 3 to 6) it is necessary to specify decay coefficients for the standing concentration waves in each zone. One can specify sufficiently large decay coefficients β_i^m to achieve high purity and high yield (Wu et al., 1998; Xie et al., 2000). However, it is convenient to specify β_i^m according to the desired yield of each component.

An approach that can be used to link product yield to the values of β_i^m is proposed here. The approach is based on simple material balances around the inlet and outlet ports. For each component, it is assumed that the concentration profile is flat in a zone in which it is neither standing nor "pinched." The feed port is treated as a mixing junction between zones II and III and the feed inlet. The desorbent port is treated as a mixing junction between zones I and IV and the desorbent inlet. To use this approach, it is necessary to specify the desired product yield of each component in the mixture. This can be denoted by Y_i for each component i. Figure 23 shows schematic column profiles for the standing components in a four-zone SMB. For each component that is desired to be recovered in the raffinate,

$$C_i^R = \frac{F C_i^F Y_i}{R}, \ \forall i \in \{1,\ldots,j\} \tag{58}$$

$$C_i^E = \frac{F C_i^F (1-Y_i)}{E}, \ \forall i \in \{1,\ldots,j\} \tag{59}$$

$$C_i^{FP} = \frac{F^{III} C_i^R - F C_i^F}{F^{II}}, \ \forall i \in \{1,\ldots,j\} \tag{60}$$

$$C_i^{DP} = \frac{F^{I}}{F^{IV}} C_i^E, \ \forall i \in \{1,\ldots,j\} \tag{61}$$

where $C^R{}_i$ is the time-averaged concentration of component i at the raffinate port, F is the feed flow rate, $C^F{}_i$ is the concentration of i in the feed solution, $C^E{}_i$ is the concentration of i in the extract, $C^{FP}{}_i$ is the concentration of i at the feed port (which is considered to be diluted from the true feed because of recycle from zone II), C_i^{DP} is the concentration of i at the desorbent port, R is the raffinate flow rate, and E is the extract flow rate. For each component desired to be recovered in the extract

$$C_i^R = \frac{F C_i^F (1-Y_i)}{R}, \ \forall i \in \{j+1,\ldots,N\} \tag{62}$$

$$C_i^E = \frac{F C_i^F Y_i}{E}, \ \forall i \in \{j+1,\ldots,N\} \tag{63}$$

$$C_i^{FP} = \frac{F^{II} C_i^E + F C_i^F}{F^{III}}, \ \forall i \in \{j+1,\ldots,N\} \tag{64}$$

$$C_i^{DP} = \frac{F^{IV}}{F^{I}} C_i^R, \ \forall i \in \{j+1,\ldots,N\} \tag{65}$$

Equations 62 to 65 can be applied to solve for the concentration of each component at each port, which in turn can be used to calculate the decay coefficient for each zone:

$$\beta_N{}^{\mathrm{I}} = \ln\left(\frac{C_N{}^{E}}{C_N{}^{DP}}\right) \tag{66}$$

$$\beta_j{}^{\mathrm{II}} = \ln\left(\frac{C_j{}^{FP}}{C_j{}^{E}}\right) \tag{67}$$

$$\beta_{j+1}{}^{\mathrm{III}} = \ln\left(\frac{C_{j+1}{}^{FP}}{C_{j+1}{}^{R}}\right) \tag{68}$$

$$\beta_1{}^{\mathrm{IV}} = \ln\left(\frac{C_1{}^{R}}{C_1{}^{DP}}\right) \tag{69}$$

The solution of the four zone flow rates and the switching time (Eqs. 3 to 6 and 21) is iterative. The initial guess of the zone flow rates and switching time come from the equilibrium equations (Eqs. 17 to 20). These parameters are used to determine mass-transfer parameters for each component in each zone, which are in turn used to re-calculate the zone flow rates and switching time. The calculation and re-substitution is continued until the flow rates and switching time change by less than 0.01% at each step.

Nomenclature

a_i = linear equilibrium distribution coefficient of component i, ml/ml S.V.

c_i = mobile-phase concentration of component i (a function of z and t), mg/ml

c_{pi} = pore-phase concentration of component i (a function of r and t), mg/ml

$C_{i,\max}{}^{m}$ = maximum time-averaged concentration of component i in zone m, mg/ml

$C_{i,\min}{}^{m}$ = minimum time-averaged concentration of component i in zone m, mg/ml

C_i^{DP} = concentration of component i at the desorbent port, mg/ml

C_i^{E} = concentration of component i at the extract port, mg/ml

C_i^{FP} = concentration of component i at the feed port, mg/ml

C_i^{R} = concentration of component i at the raffinate port, mg/ml

D = desorbent flow rate, ml/min

D_{pi} = intraparticle diffusivity of component i, cm^2/min

D_A = desorbent flow rate to ring A in a two-ring SMB, ml/min

D_B = desorbent flow rate to ring B in a two-ring SMB, ml/min

D_{total} = total desorbent flow rate to a two-ring SMB, ml/min

D_i^{∞} = Brownian diffusivity of component i, cm^2/min

E = extract flow rate, ml/min

E_A = extract flow rate from ring A in a two-ring SMB, ml/min

E_{bi}^m = axial dispersion coefficient of component i in zone m, cm^2/min

F = feed flow rate, ml/min

F^m = flow rate in zone m, ml/min

F_A = feed flow rate to ring A in a two-ring SMB, ml/min

F_B = feed flow rate to ring B in a two-ring SMB, ml/min

j = component index

k_{fi}^m = film mass-transfer coefficient of component i in zone m, cm/min

K_{ei} = size-exclusion coefficient of component i

K_{fi}^m = lumped mass-transfer coefficient of component i in zone m, min^{-1}

L_c = length of an individual column, cm

L^m = length of zone m, cm

n = number of port switches

N = numbering index of highest-affinity component

N_c^m = number of columns in zone m

$P \equiv (1 - \varepsilon_b)/\varepsilon_b$ = particle-mobile fluid phase ratio

q_i = solid-phase concentration of component i (a function of r and t), mg/ml S.V.

R = raffinate flow rate, ml/min

R_p = particle radius, cm

S = column cross-sectional area, cm^2

S.V. = solid volume

t = time, min

t_p = time required to inject pulse, min

t_{ri} = retention time of component i, min

t_s = switching time, min

t_{0i} = elution time of component i neglecting adsorption, min

u_0^m = liquid interstitial velocity in zone m, cm/min

V_c = total column volume (particles + voids), ml

Y_i = yield of component i in its desired product port

z = axial distance along the SMB, cm

z_0^m = position of furthest-upstream point in zone m, cm

β_i^m = decay factor of standing wave i in zone m

$\delta_i \equiv K_{ei}\varepsilon_p + (1 - \varepsilon_p)a_i$ = retention factor of component i

Δ_i^m = mass-transfer correction term for standing component i in zone m

ε_b = intraparticle void fraction

ε_p = interparticle void fraction

v = solid movement velocity, cm/min

v_A = solid movement velocity for ring A in a two-ring SMB, cm/min

v_B = solid movement velocity for ring B in a two-ring SMB, cm/min

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What is claimed is:

1) A process for chromatographically separating a desired component or fraction other than insulin from a multicomponent mixture, under linear isotherm conditions wherein non-negligible mass transfer resistances are observed, comprising:
   a) providing a simulated moving bed that comprises a first ring and a first desorbent stream;
   b) providing a first feed stream that comprises the desired component or fraction and a first component or fraction;
   c) introducing the first desorbent stream and the first feed stream to the first ring under conditions sufficient to separate the desired component or fraction from the first component or fraction, and to minimize desorbent use; and
   d) withdrawing the first component or fraction as a raffinate or extract from the SMB.

2) The method of claim 1 wherein the desorbent use is less than 110% of the minimum use defined by the standing wave design.

3) The method of claim 1 wherein the desorbent use is less than 105% of the minimum desorbent use defined by the standing wave design.

4) The method of claim 1 wherein the mass transfer correction term associated with the mass transfer effects is more than 20% of the ideal mobile phase velocity in one or more of the zones.

5) The method of claim 1 wherein the mass transfer correction term associated with the mass transfer effects is more than 5% of the ideal mobile phase velocity in one or more of the zones.

6) The method of claim 1 wherein:
   a) the first ring comprises 4 zones and 5 or more columns, or 5 zones and 6 or more columns;
   b) the columns are allocated among the zones in a manner that optimizes the economic efficiency of the SMB for a defined mobile phase velocity in one or more of the columns, and a defined yield and purity of the desired component or fraction.

7) The method of claim 1 further comprising:

a) introducing a second desorbent stream and the desired component or fraction from the first ring to a second ring, under conditions sufficient to separate the desired component or fraction from the second component or fraction, and to minimize desorbent use from the second desorbent stream; and

b) withdrawing from the second ring an extract or raffinate that comprises the desired component or fraction separated from the second component or fraction.

8) The method of claim 7 wherein the second component or fraction is allowed to distribute through the first ring.

9) The method of claim 7 wherein the difference between the affinity of the desired component or fraction and the affinity of the first component or fraction for the adsorbent in the first ring, is greater than the difference between the affinity of the desired component or fraction and the affinity of the second component or fraction for the adsorbent in the second ring.

10) The method of claim 1 wherein the separation is hindered by non-negligible fronting and/or extra-column effects.

11) The method of claim 10 wherein the fronting and/or extra-column effects cause the mass transfer correction term in one or more of the zones to change by more than 20%.

12) The method of claim 10 wherein the fronting and/or extra-column effects cause the mass transfer correction term in one or more of the zones to change by more than 50%.

13) The method of claim 1 wherein the mobile phase velocity in one or more of the columns approaches the maximum for the column.

14) The method of claim 1 wherein the desired component or fraction is the fastest or slowest of the multicomponent mixture.

15) The method of claim 1 wherein the first ring comprises 5 zones.

16) The method of claim 1 wherein the SMB comprises a first ring A, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, a split is desired between components j and j+1, and the equations assume standing wave conditions in the first ring for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j+1 in zone IIA;

c) the adsorption wave of component j in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

17) The method of claim 1 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component *j*-1 in zone IIA;

c) the adsorption wave of component j in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

e) the desorption wave of component N in zone IB;

f) the desorption wave of component j in zone IIB;

g) the adsorption wave of component *j*+1 in zone IIIB; and

h) the adsorption wave of component j in zone IVB.

18) The method of claim 1 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the adsorption wave of component j +1 in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

e) the desorption wave of component j in zone IB;

f) the desorption wave of component *j*-1 in zone IIB;

g) the adsorption wave of component j in zone IIIB; and

h) the adsorption wave of component 1 in zone IVB.

19) The method of claim 1 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component j in zone IA;

b) the desorption wave of component *j*-1 in zone IIA;

c) the adsorption wave of component j in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

e) the desorption wave of component N in zone IB;

f) the desorption wave of component j in zone IIB;

g) the adsorption wave of component j+1 in zone IIIB; and

h) the adsorption wave of component j in zone IVB.

20) The method of claim 1 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the adsorption wave of component j+1 in zone IIIA;

d) the adsorption wave of component j in zone IVA;

e) the desorption wave of component j in zone IB;

f) the desorption wave of component j-1 in zone IIB;

g) the adsorption wave of component j in zone IIIB; and

h) the adsorption wave of component 1 in zone IVB.

21) The method of claim 1 wherein the SMB comprises a five zone ring A and a four zone ring B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the desorption wave of component j-1 in zone IIIA;

d) the adsorption wave of component j in zone IVA;

e) the adsorption wave of component 1 in zone VA;

f) the desorption wave of component N in zone IB;

g) the desorption wave of component j in zone IIB;

h) the adsorption wave of component j+1 in zone IIIB; and

i) the adsorption wave of component j in zone IVB.

22) The method of claim 1 wherein the SMB comprises a five zone ring A and a four zone ring B, the mixture comprises components numbered 1 . . . j . . .N, in order of

increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the adsorption wave of component j+1 in zone IIIA;

d) the adsorption wave of component j in zone IVA;

e) the adsorption wave of component 1 in zone VA;

f) the desorption wave of component j in zone IB;

g) the desorption wave of component j-1 in zone IIB;

h) the adsorption wave of component j in zone IIIB; and

i) the adsorption wave of component 1 in zone IVB.

23) A method for chromatographically purifying a desired component or fraction other than insulin using a SMB, under linear isotherm conditions wherein non-negligible mass transfer resistances are observed, comprising:

a) providing a simulated moving bed that comprises a stationary phase, a first desorbent stream, and a first ring that comprises 4 zones and 5 or more columns, or 5 zones and 6 or more columns;

b) providing a feed stream that comprises the desired component or fraction and a first component or fraction;

c) introducing the desorbent stream and the feed stream to the SMB under conditions sufficient to separate the desired component or fraction from the first component or fraction; and

d) withdrawing from desired component or fraction from the first ring in the extract or raffinate;

e) wherein the columns are allocated among the zones in a manner that optimizes economic efficiency, for a defined yield and purity of the desired component or fraction.

24) The method of claim 23 wherein the feed stream comprises three or more components.

25) The method of claim 23 for separating an intermediate fraction from the multicomponent mixture, wherein (i) the simulated moving bed further comprises a second ring that comprises 4 zones and 4 or more columns, and (ii) the feed stream further comprises a second component or fraction;

a) further comprising:

b) providing a second desorbent stream;

c) introducing the second desorbent stream and the desired component or fraction from the first ring to the second ring as a second feed stream, under conditions sufficient to separate the desired component or fraction from the second component or fraction;

d) further wherein the 5 or more columns in the second ring are allocated among the zones in a manner that optimizes economic efficiency.

26) The method of claim 23 wherein the desorbent use is minimized for the rate of feed to the SMB.

27) The method of claim 23 wherein the throughput is maximized for the rate of desorbent feed to the SMB.

28) The method of claim 23 wherein the second component or fraction is allowed to distribute through the first ring.

29) The method of claim 23 wherein the difference between the affinity of the desired component or fraction and the affinity of the first component or fraction for the adsorbent in the first ring, is greater than the difference between the affinity of the desired component or fraction and the affinity of the second component or fraction for the adsorbent in the second ring.

30) The method of claim 23 wherein the separation is hindered by non-negligible fronting and/or extra-column effects.

31) The method of claim 23 wherein the mobile phase velocity in one or more of the columns approaches the maximum for the column.

32) The method of claim 23 wherein the first ring comprises five or more zones and six or more columns.

33) A method for chromatographically separating a component or fraction other than insulin from fast and slow fractions and/or components under linear isotherm conditions comprising:

a) providing a simulated moving bed that comprises first and second rings and first and second stationary phases;

b) providing first and second desorbent streams;

c) providing a first feed stream that comprises a fast fraction or component, an intermediate fraction or component, and a slow fraction or component;

d) introducing the first desorbent stream and the first feed stream to the first ring under conditions sufficient to separate the intermediate fraction from the fast or slow fraction or component;

e) allowing the fast or slow fraction or component to distribute in the first ring;

f) withdrawing from the first ring the intermediate fraction or component separated from the fast or slow fraction or component;

g) introducing the second desorbent stream and the intermediate fraction or component from the first ring to the second ring as a second feed stream, under conditions sufficient to separate the intermediate fraction from the fast or slow fraction or component; and

h) withdrawing from the second ring the intermediate fraction or component separated from the fast and slow fractions and/or components.

34) The method of claim 33 wherein:

a) the first desorbent stream and first feed stream are introduced to the first ring under conditions to minimize the first desorbent use; and

b) the second desorbent stream and the second feed stream are introduced to the second ring under conditions to minimize the second desorbent use.

35) The method of claim 33 wherein:

a) the first ring comprises 4 zones and 5 or more columns, or 5 zones and 6 or more columns;

b) the columns are allocated among the zones in a manner that optimizes economic efficiency.

36) The method of claim 33 wherein the separation is hindered by non-negligible fronting and/or extra-column effects.

37) The method of claim 33 wherein the mobile phase velocity in one or more of the columns approaches the maximum for the column.

38) The method of claim 33 wherein non-negligible mass transfer resistances are observed.

39) The method of claim 33 wherein non-negligible mass transfer resistances are not observed.

40) A method of designing an SMB for separating a desired fraction or component other than insulin from a first fraction or component, in a multicomponent mixture, comprising:

a) providing equations that relate the design, operating, and intrinsic engineering parameters of a SMB that displays linear isotherms and non-negligible mass transfer resistances, wherein the equations assume standing wave conditions for all zones of the SMB;

b) prescribing a first set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to solve the equations for resolving the multicomponent mixture in a first SMB; and

c) resolving the equations.

41) The method of claim 40 wherein the SMB comprises a first ring A, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, a split is desired between components j and j+1, and the equations assume standing wave conditions in the first ring for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component *j*+1 in zone IIA;

c) the adsorption wave of component j in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

42) The method of claim 40 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component *j*-1 in zone IIA;

c) the adsorption wave of component j in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

e) the desorption wave of component N in zone IB;

f) the desorption wave of component j in zone IIB;

g) the adsorption wave of component *j*+1 in zone IIIB; and

h) the adsorption wave of component j in zone IVB.

43) The method of claim 40 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the adsorption wave of component j +1 in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

e) the desorption wave of component j in zone IB;

f) the desorption wave of component *j*-1 in zone IIB;

g) the adsorption wave of component j in zone IIIB; and

h) the adsorption wave of component 1 in zone IVB.

44) The method of claim 40 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component j in zone IA;

b) the desorption wave of component *j*-1 in zone IIA;

c) the adsorption wave of component j in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

e) the desorption wave of component N in zone IB;

f) the desorption wave of component j in zone IIB;

g) the adsorption wave of component *j*+1 in zone IIIB; and

h) the adsorption wave of component j in zone IVB.

45) The method of claim 40 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the adsorption wave of component *j*+1 in zone IIIA;

d) the adsorption wave of component j in zone IVA;

e) the desorption wave of component j in zone IB;

f) the desorption wave of component *j*-1 in zone IIB;

g) the adsorption wave of component j in zone IIIB; and

h) the adsorption wave of component 1 in zone IVB.

46) The method of claim 40 wherein the SMB comprises a five zone ring A and a four zone ring B, the mixture comprises components numbered 1 . . . j . . .N, in order of

increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the desorption wave of component *j*-1 in zone IIIA;

d) the adsorption wave of component j in zone IVA;

e) the adsorption wave of component 1 in zone VA;

f) the desorption wave of component N in zone IB;

g) the desorption wave of component j in zone IIB;

h) the adsorption wave of component *j*+1 in zone IIIB; and

i) the adsorption wave of component j in zone IVB.

47) The method of claim 40 wherein the SMB comprises a five zone ring A and a four zone ring B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the adsorption wave of component *j*+1 in zone IIIA;

d) the adsorption wave of component j in zone IVA;

e) the adsorption wave of component 1 in zone VA;

f) the desorption wave of component j in zone IB;

g) the desorption wave of component *j*-1 in zone IIB;

h) the adsorption wave of component j in zone IIIB; and

i) the adsorption wave of component 1 in zone IVB.

48) The method of claim 41 wherein components 1 and *j* are the same.

49) The method of claim 41 wherein components *j*+1 and *N* are the same.

50) The method of claim 40 wherein the equations define the minimum rate of desorbent use for a given rate of feed.

51) The method of claim 40 wherein the first set of design and operating parameters is sufficient to determine the maximum allowable pressure drop across the columns of the first and second SMBs, and the equations are resolved based upon a maximum allowable mobile phase velocity in one or more of the zones.

52) The method of claim 40 wherein the equations are resolved based upon a maximum allowable mobile phase velocity in zone I.

53) The method of claim 40 wherein the separation is not hindered by non-negligible mass transfer resistances, and the equations relate:

a) feed flow rate;

b) desorbent flow rate;

c) zone flow rates;

d) port movement velocity; and

e) component retention rates.

54) The method of claim 40 wherein the separation is hindered by non-negligible mass transfer resistances, and the equations relate:

a) zone length;

b) feed flow rate;

c) desorbent flow rate;

d) zone flow rates;

e) port movement velocity;

f) product purity and yield;

g) mass transfer resistances; and

h) component retention rates.

55) A method of optimizing a SMB system that displays linear isotherms comprising:

a) providing equations that relate the design, operating, and intrinsic engineering parameters of a SMB that displays linear isotherms;

b) prescribing a first set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to resolve the equations for separating a binary or multicomponent mixture other than a mixture comprising insulin in a first SMB;

c) prescribing a second set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to resolve the equations for separating the binary or multicomponent mixture in a second SMB; and

d) evaluating and comparing the economic efficiency of the first and second SMBs.

56) The method of claim 55 wherein the SMB comprises a first ring A, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the

stationary phase, a split is desired between components j and j+1, and the equations assume standing wave conditions in the first ring for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j+1 in zone IIA;

c) the adsorption wave of component j in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

57) The method of claim 55 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j-1 in zone IIA;

c) the adsorption wave of component j in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

e) the desorption wave of component N in zone IB;

f) the desorption wave of component j in zone IIB;

g) the adsorption wave of component j+1 in zone IIIB; and

h) the adsorption wave of component j in zone IVB.

58) The method of claim 55 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the adsorption wave of component j +1 in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

e) the desorption wave of component j in zone IB;

f) the desorption wave of component j-1 in zone IIB;

g) the adsorption wave of component j in zone IIIB; and

h) the adsorption wave of component 1 in zone IVB.

59) The method of claim 55 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing

affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component j in zone IA;

b) the desorption wave of component *j*-1 in zone IIA;

c) the adsorption wave of component j in zone IIIA;

d) the adsorption wave of component 1 in zone IVA;

e) the desorption wave of component N in zone IB;

f) the desorption wave of component j in zone IIB;

g) the adsorption wave of component *j*+1 in zone IIIB; and

h) the adsorption wave of component j in zone IVB.

60) The method of claim 55 wherein the SMB comprises two four zone rings A and B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the adsorption wave of component *j*+1 in zone IIIA;

d) the adsorption wave of component j in zone IVA;

e) the desorption wave of component j in zone IB;

f) the desorption wave of component *j*-1 in zone IIB;

g) the adsorption wave of component j in zone IIIB; and

h) the adsorption wave of component 1 in zone IVB.

61) The method of claim 55 wherein the SMB comprises a five zone ring A and a four zone ring B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the desorption wave of component *j*-1 in zone IIIA;

d) the adsorption wave of component j in zone IVA;

e) the adsorption wave of component 1 in zone VA;

f) the desorption wave of component N in zone IB;

g) the desorption wave of component j in zone IIB;

h) the adsorption wave of component j+1 in zone IIIB; and

i) the adsorption wave of component j in zone IVB.

62) The method of claim 55 wherein the SMB comprises a five zone ring A and a four zone ring B, the mixture comprises components numbered 1 . . . j . . .N, in order of increasing affinity for the stationary phase, purified component j is desired, and the equations assume standing wave conditions in the first and second rings for:

a) the desorption wave of component N in zone IA;

b) the desorption wave of component j in zone IIA;

c) the adsorption wave of component j+1 in zone IIIA;

d) the adsorption wave of component j in zone IVA;

e) the adsorption wave of component 1 in zone VA;

f) the desorption wave of component j in zone IB;

g) the desorption wave of component j-1 in zone IIB;

h) the adsorption wave of component j in zone IIIB; and

i) the adsorption wave of component 1 in zone IVB.

63) The method of claim 55 wherein the equations define the minimum desorbent use for a given feed flow rate.

64) The method of claim 55 wherein the first and second sets of design and operating parameters are sufficient to determine the maximum allowable pressure drop across the columns of the first and second SMBs, and the equations are resolved based upon a maximum mobile phase velocity in one or more of the zones.

65) The method of claim 55 wherein the equations are resolved based upon a maximum mobile phase velocity in zone I.

66) The method of claim 55 wherein the economic efficiency is determined by reference to desorbent consumption.

67) The method of claim 55 wherein the economic efficiency is determined by reference to throughput.

68) The method of claim 55 further comprising:

a) prescribing a third set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to resolve the equations for a third SMB; and

b) evaluating and comparing the economic efficiency of the third SMB.

69) The method of claim 55 wherein the allocation of columns varies between the first and second sets of design and operating parameters.

70) The method of claim 55 wherein the number of columns varies between the first and second sets of design and operating parameters.

71) The method of claim 55 wherein the length of the columns varies between the first and second sets of design and operating parameters.

72) The method of claim 55 wherein the adsorbent particle size varies between the first and second sets of design and operating parameters.

73) The method of claim 55 wherein the adsorbent type varies between the first and second sets of design and operating parameters.

74) The method of claim 55 wherein the desorbent varies between the first and second sets of design and operating parameters.

75) The method of claim 55 wherein the splitting strategy varies between the first and second sets of design and operating parameters.

76) The method of claim 55 wherein the feed flow rate varies between the first and second sets of design and operating parameters.

77) The method of claim 55 wherein the product purity and yield varies between the first and second sets of design and operating parameters.

78) The method of claim 55 wherein the mixture comprises two components.

79) The method of claim 55 wherein the mixture comprises three or more components.

80) The method of claim 55 wherein the separation is inhibited by non-negligible mass transfer effects.

81) The method of claim 55 wherein the separation is not inhibited by non-negligible mass transfer effects.

82) The method of claim 55 wherein the separation is not hindered by non-negligible mass transfer resistances, and the equations relate:

a) feed flow rate;

b) desorbent flow rate;

c) zone flow rates;

d) port movement velocity; and

e) component retention rates.

83) The method of claim 55 wherein the separation is hindered by non-negligible mass transfer resistances, and the equations relate:

a) zone length;

b) feed flow rate;

c) desorbent flow rate;

d) zone flow rates;

e) port movement velocity;

f) product purity and yield;

g) mass transfer resistances; and

h) component retention rates.

84) A method of designing and operating a SMB for separating a desired component or fraction other than insulin from a fast component or fraction and a slow component or fraction, wherein the SMB comprises first and second rings, comprising:

a) providing splitting rules which provide:

i) when only the desired component or fraction is purified, allowing the fast or slow component or fraction to distribute in the first ring;

ii) when the fast and/or slow component or fraction are purified, perform the easiest split in the first ring;

b) selecting a splitting strategy based upon whether one or more of the fast and/or slow components and/or fractions is purified; and

c) operating the SMB using the selected splitting strategy.

85) The method of claim 84 wherein only the desired component or fraction is purified.

86) The method of claim 84 wherein the fast and/or slow component or fraction is purified.

87) The method of claim 84 wherein non-negligible mass transfer resistances are observed.

88) The method of claim 84 wherein non-negligible mass transfer resistances are not observed.

89) A method of designing an SMB for separating a desired fraction or component other than insulin from a first fraction or component, in a multicomponent mixture, comprising:

a) providing equations that relate the design, operating, and intrinsic engineering parameters of a SMB that displays linear isotherms,

b) prescribing a first set of design and operating parameters sufficient to determine the intrinsic engineering parameters and to solve the equations for resolving the multicomponent mixture in a first SMB; and

c) resolving the equations;

d) wherein the equations define the minimum rate of desorbent use for a given rate of feed.

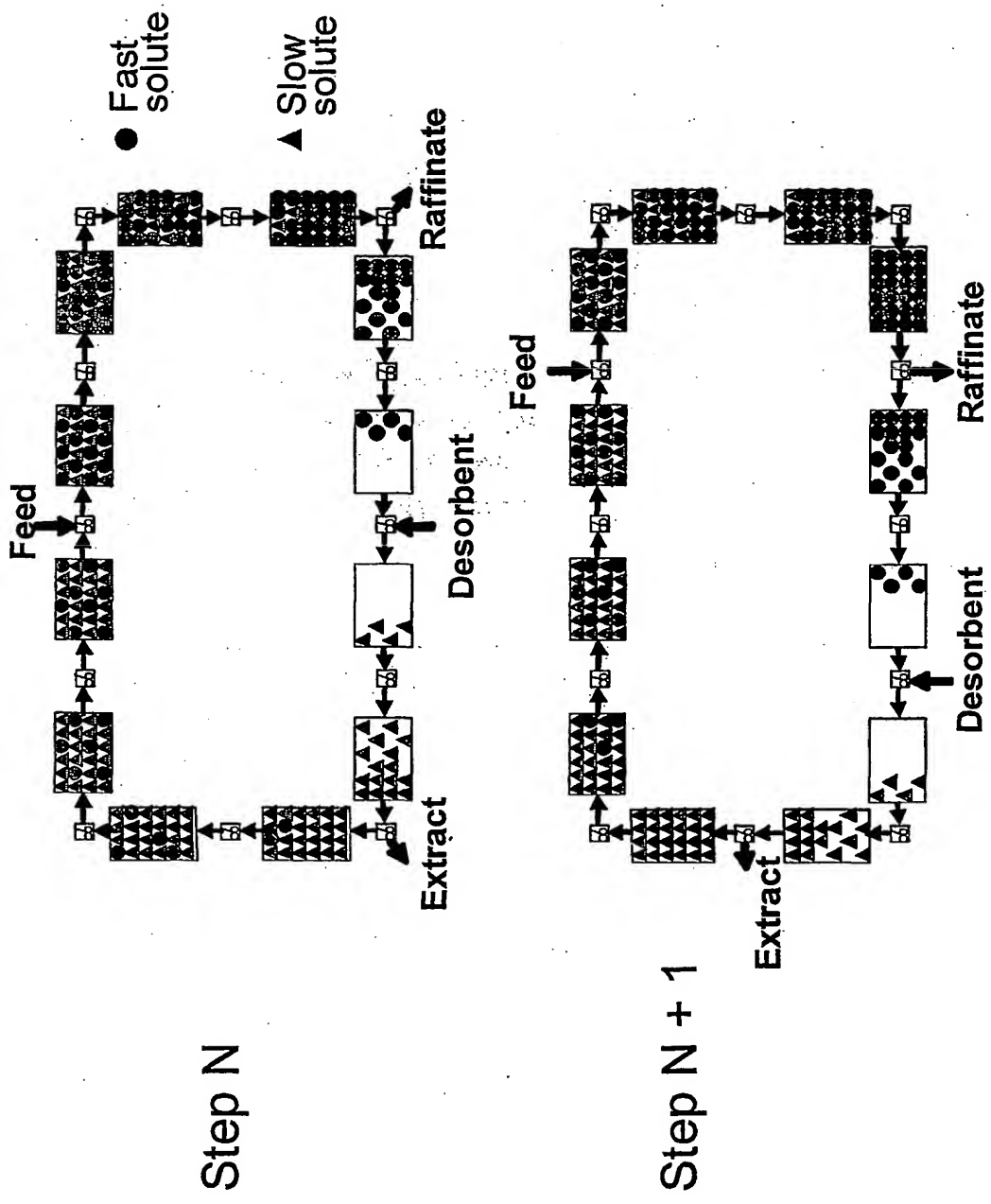

Figure 1. Schematic Diagram of a Four-Zone Simulated Moving Bed (SMB).

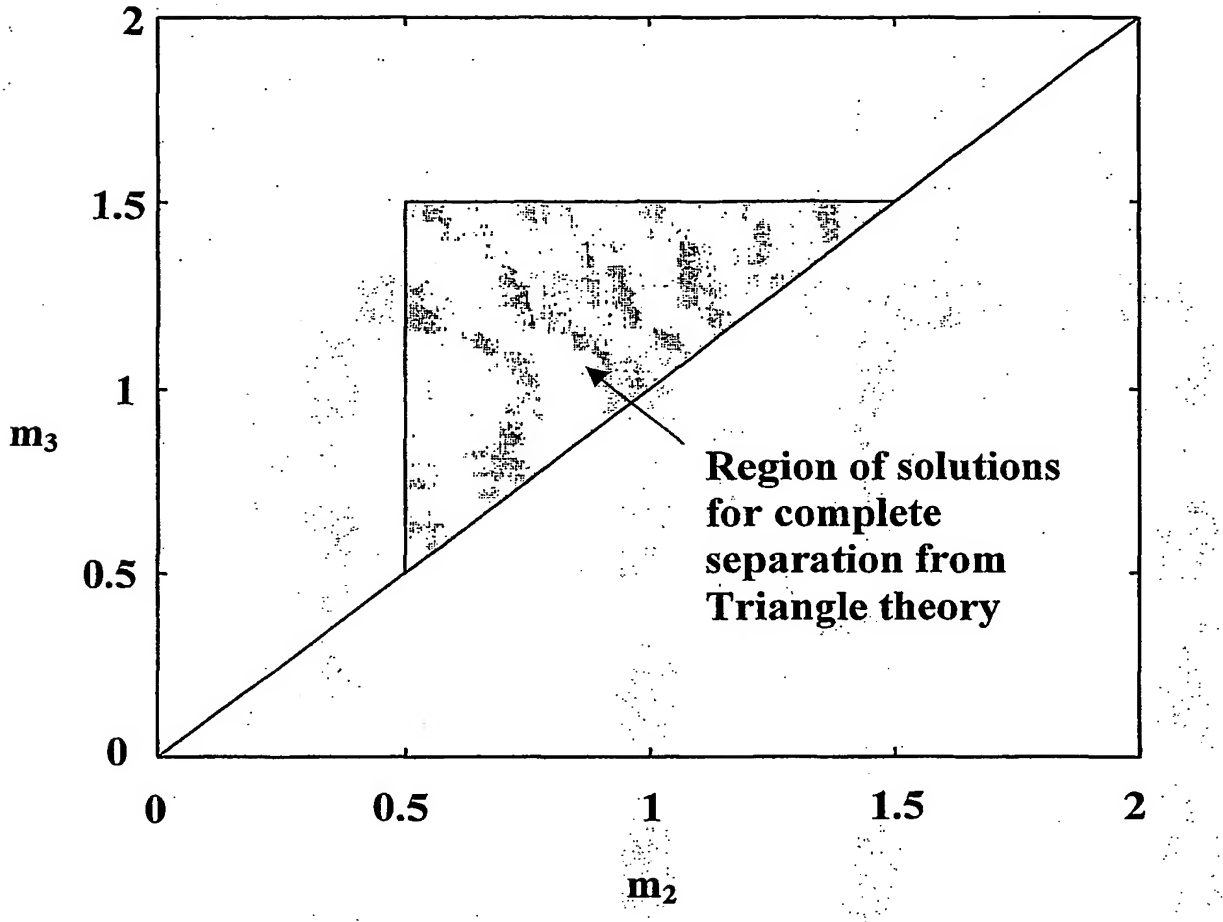

Figure 2. Triangle Theory of Ideal System with Linear Isotherm.

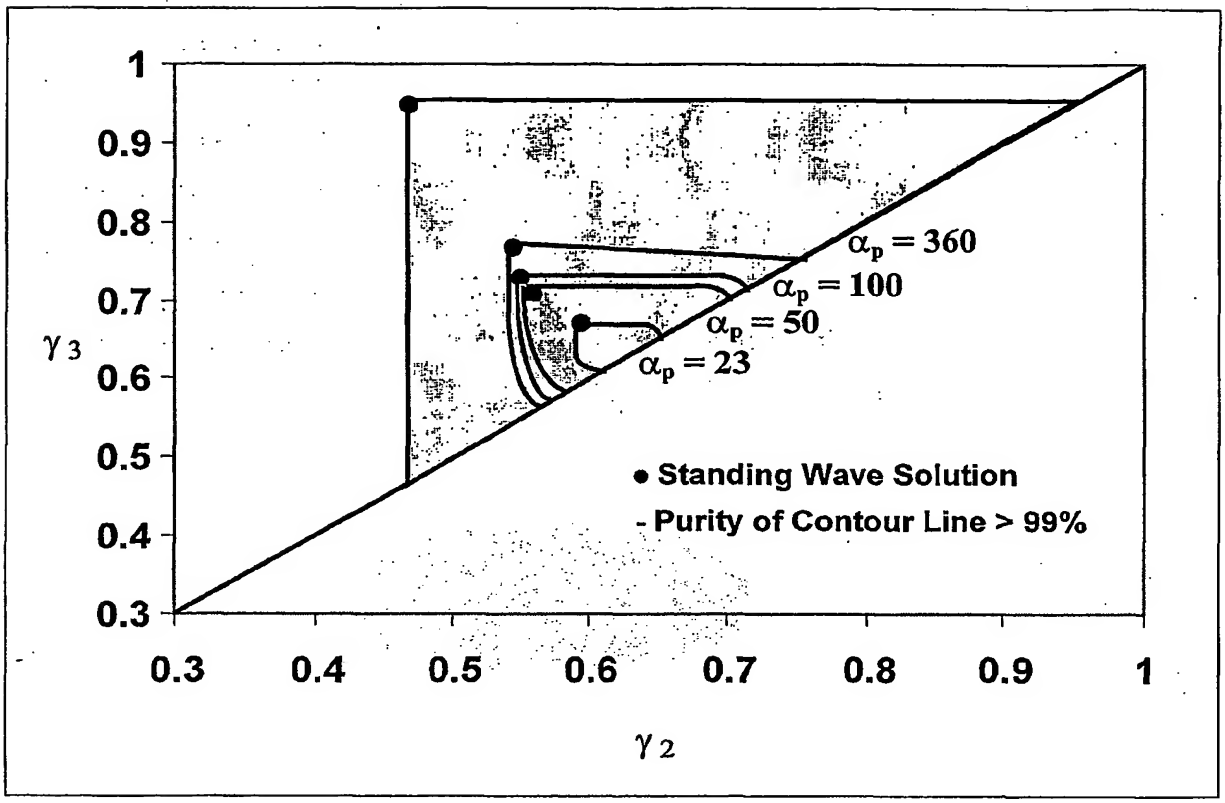

Figure 3. Nonideal System with Linear Isotherm: Comparison of Triangle Theory and Standing Wave Analysis for a Linear System

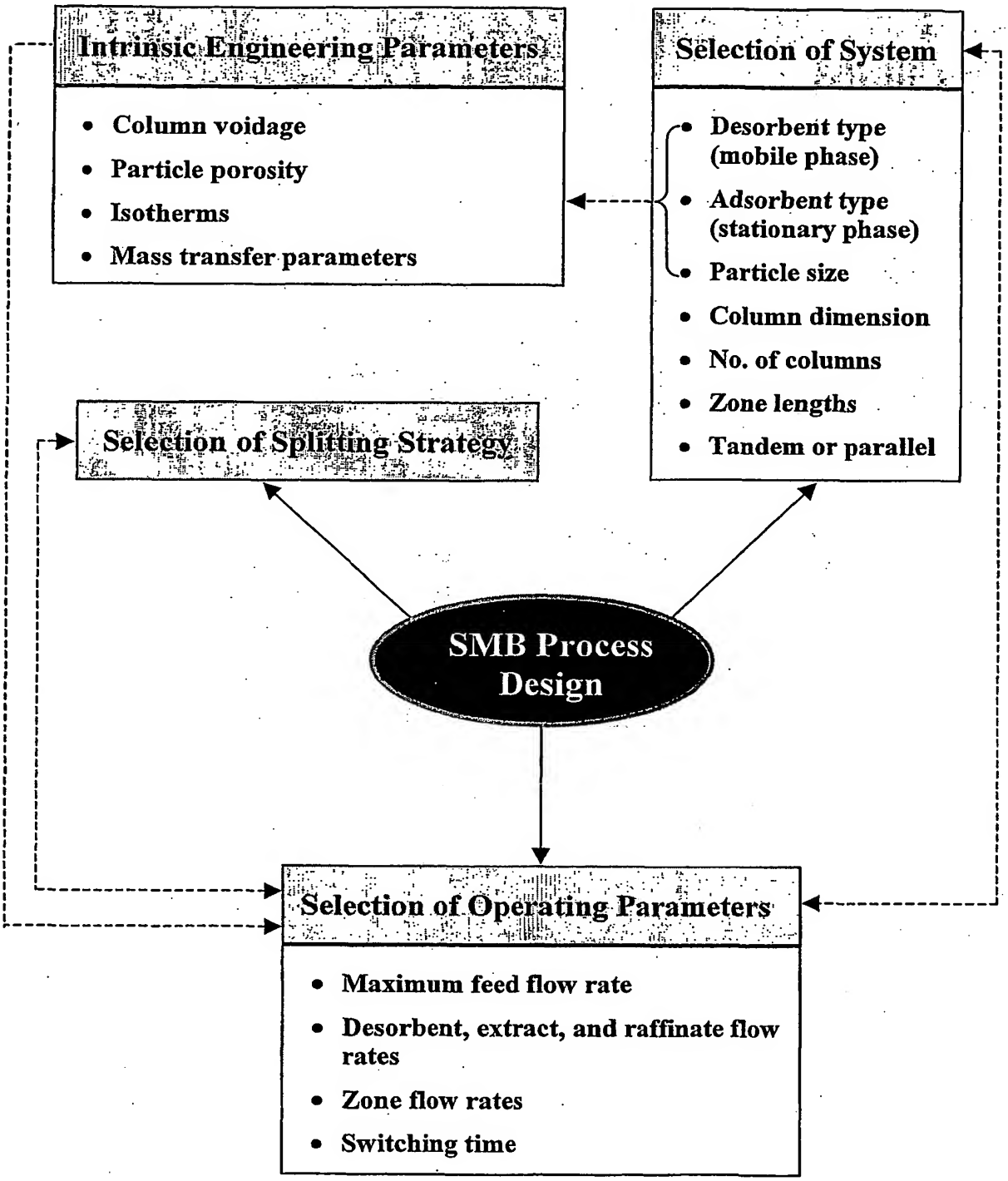

Figure 4. Parameters Involved in the SMB Process Design

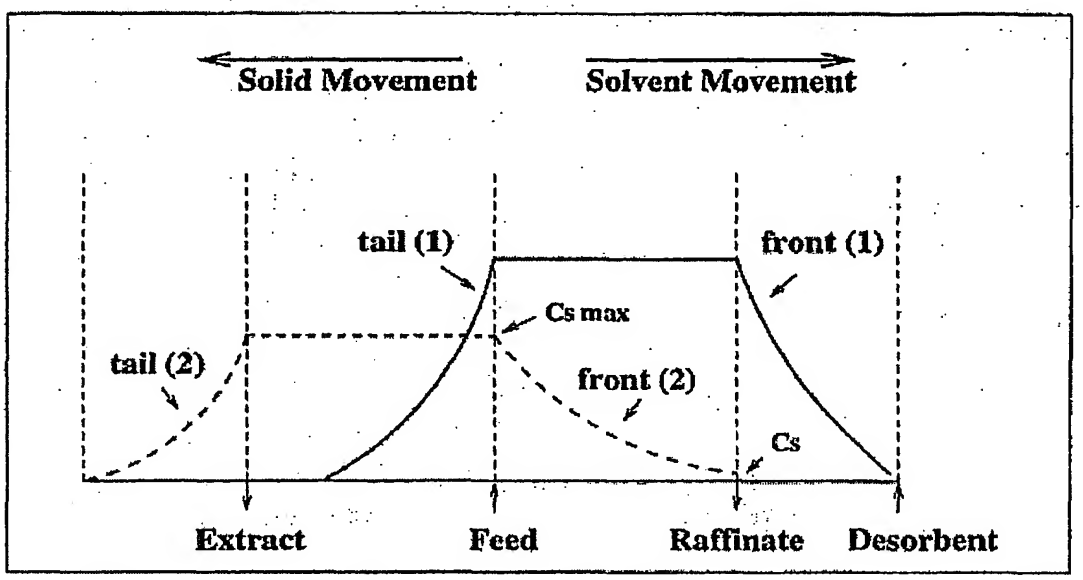

Figure 5. Standing Waves in Binary Continuous Moving Bed Systems. Solute 1 is the fast moving solute, and solute 2 is the slow moving solute.

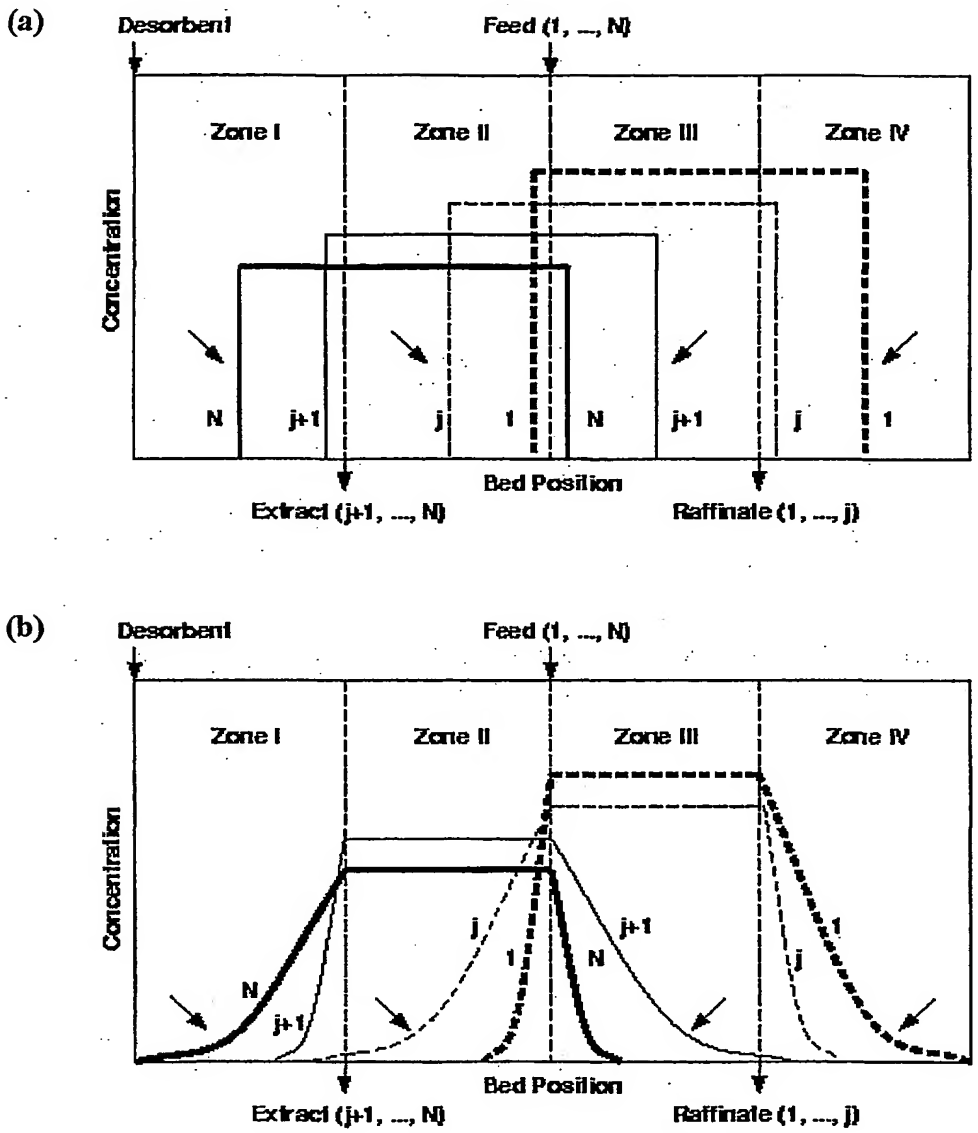

Figure 6. Standing Wave Approach for Separating an N-Component Mixture into Two Groups of Components Using a Four-Zone SMB. Angled arrows point to waves that are held standing within a given zone. (a) Ideal system; (b) Non-ideal system.

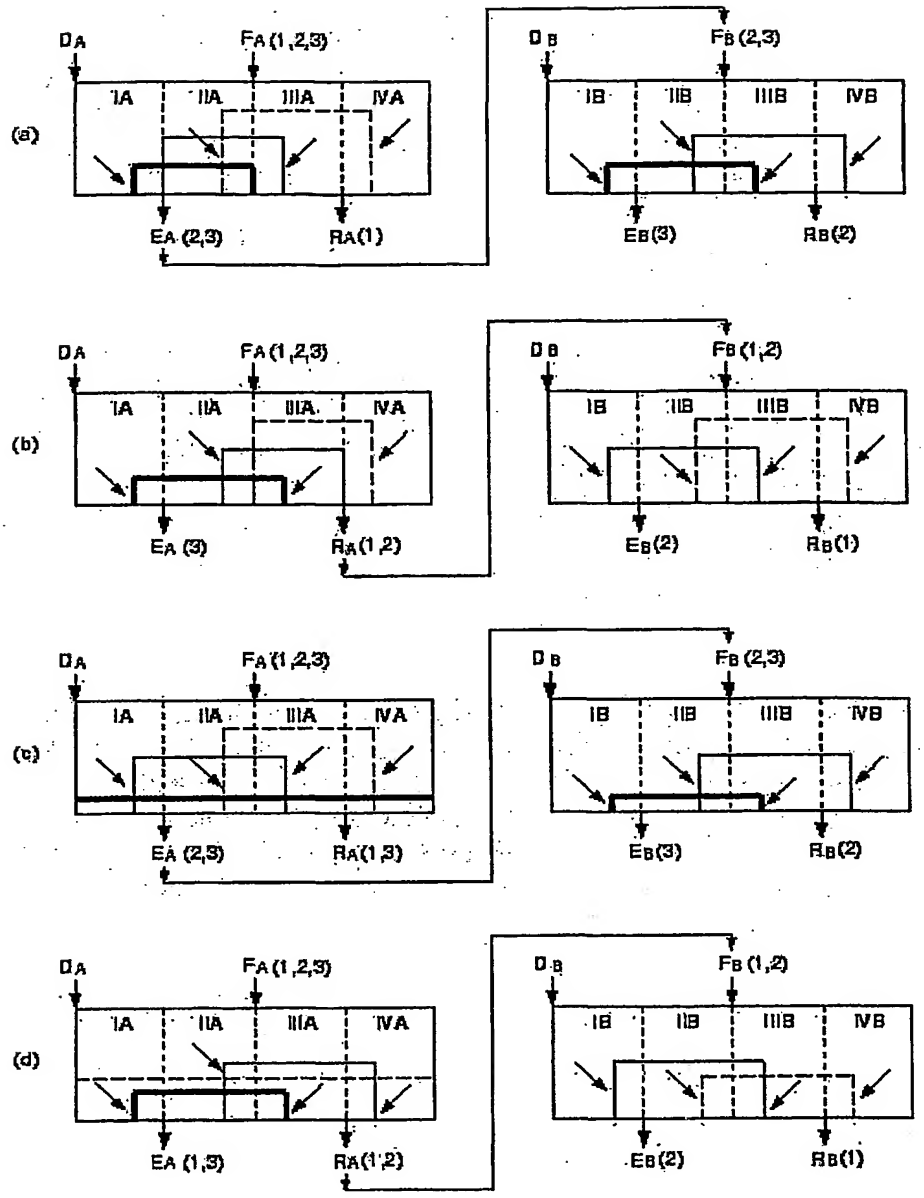

Figure 7. Strategies for Separating Components in Tandem SMB Units. Mass-transfer resistances are negligible. Dashed line: component 1; solid thin line: component 2; solid thick line: component 3. (a) Strategy S1: component 1 is separated from components 2 and 3 in the 1st ring and component 2 is separated from component 3 in the 2nd ring; (b) Strategy S2: component 3 is separated from components 1 and 2 in the 1st ring and component 2 is separated from component 1 in the 2nd ring; (c) Strategy S3: component 3 is distributed in the 1st ring and component 2 is separated from component 3 in the 2nd ring; (d) Strategy S4: component 1 is distributed in the 1st ring and component 2 is separated from component 1 in the 2nd ring;

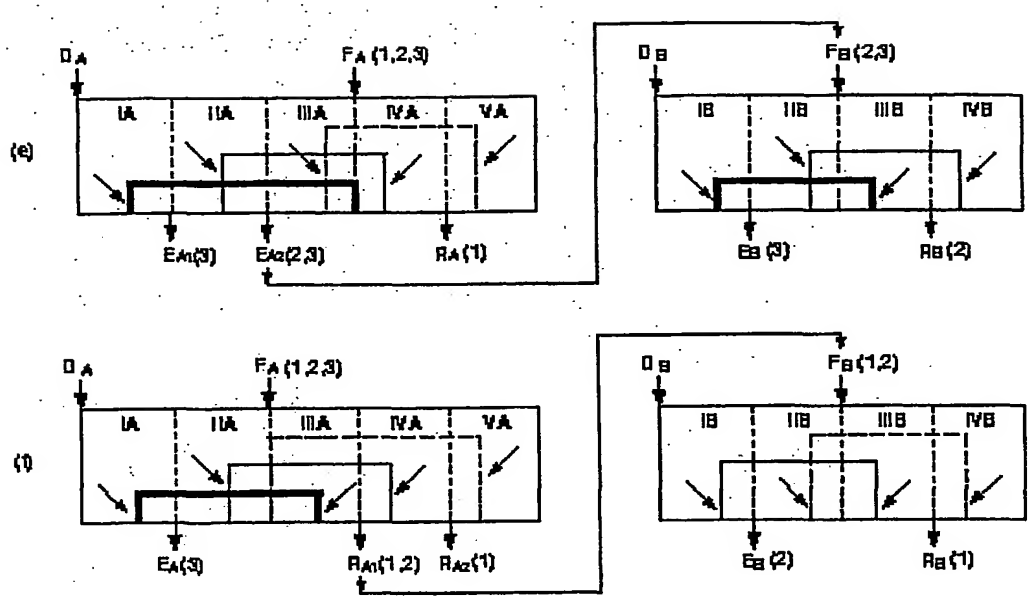

Figure 7 (cont'd). Strategies for Separating Components in Tandem SMB Units. Mass-transfer resistances are negligible. Dashed line: component 1; solid thin line: component 2; solid thick line: component 3. (e) Strategy S5: component 1 is separated from components 2 and 3 in the 1st ring (5-zone) and component 2 is separated from component 3 in the 2nd ring (4-zone); (f) Strategy S6: component 3 is separated from components 1 and 2 in the 1st ring (5-zone) and component 2 is separated from component 1 in the 2nd ring (4-zone).

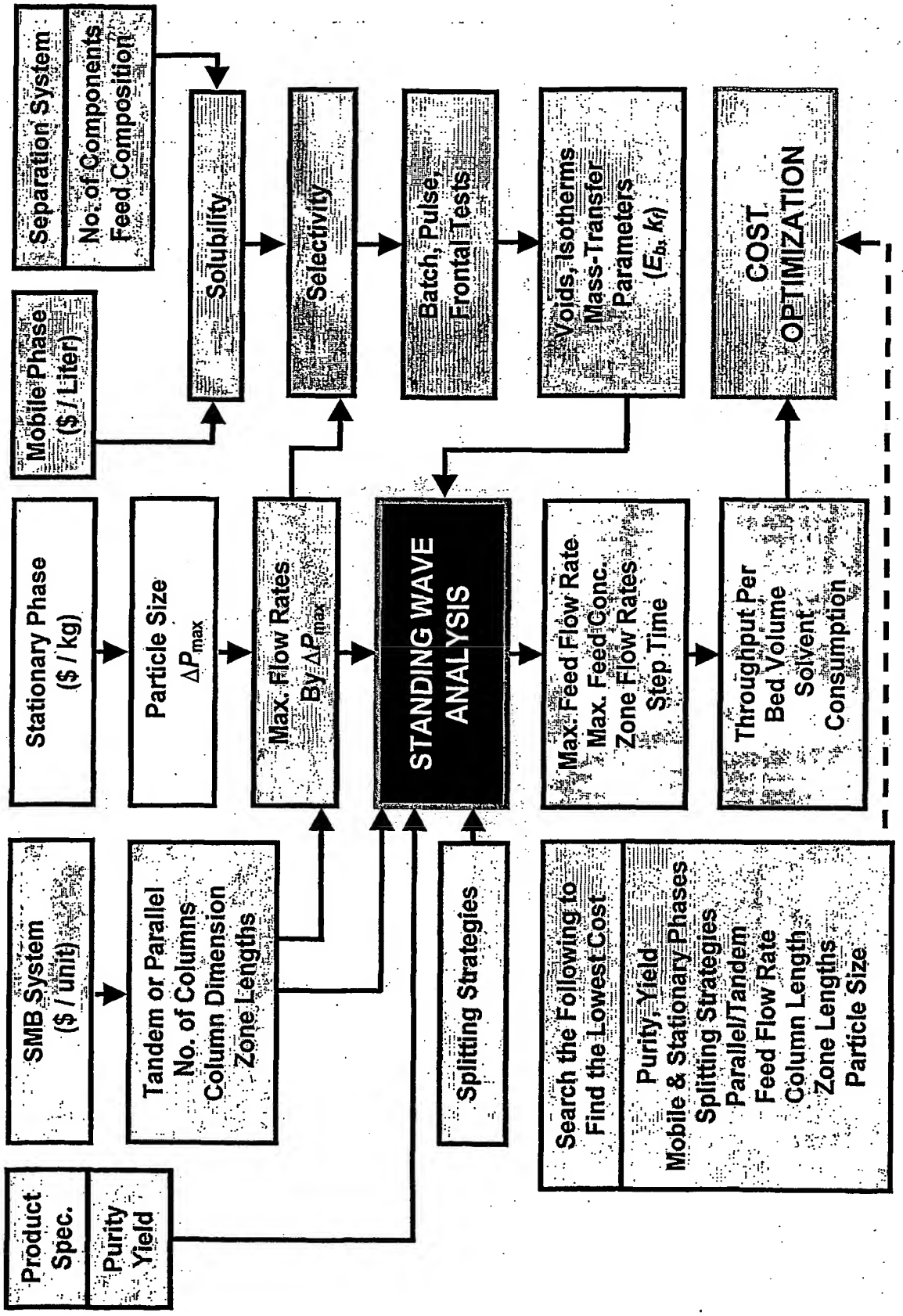

Figure 8. Cost Analysis for Simulated Moving Bed Using the Standing Wave Design

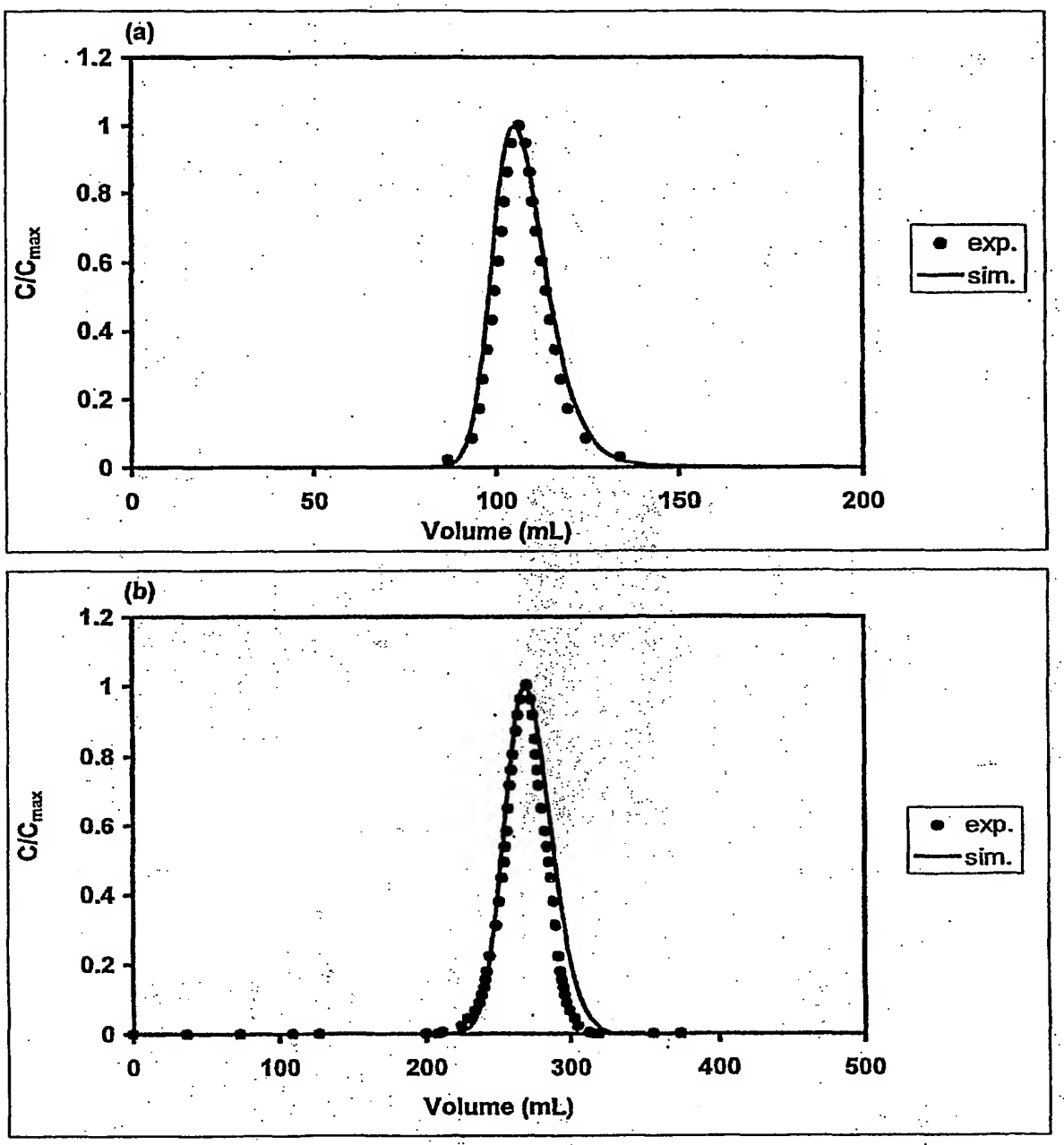

Figure 9. Experimental Data and Simulation Results of the Pulse Tests with a Lab-Scale Column. (a) Blue dextran; (b) NaCl.

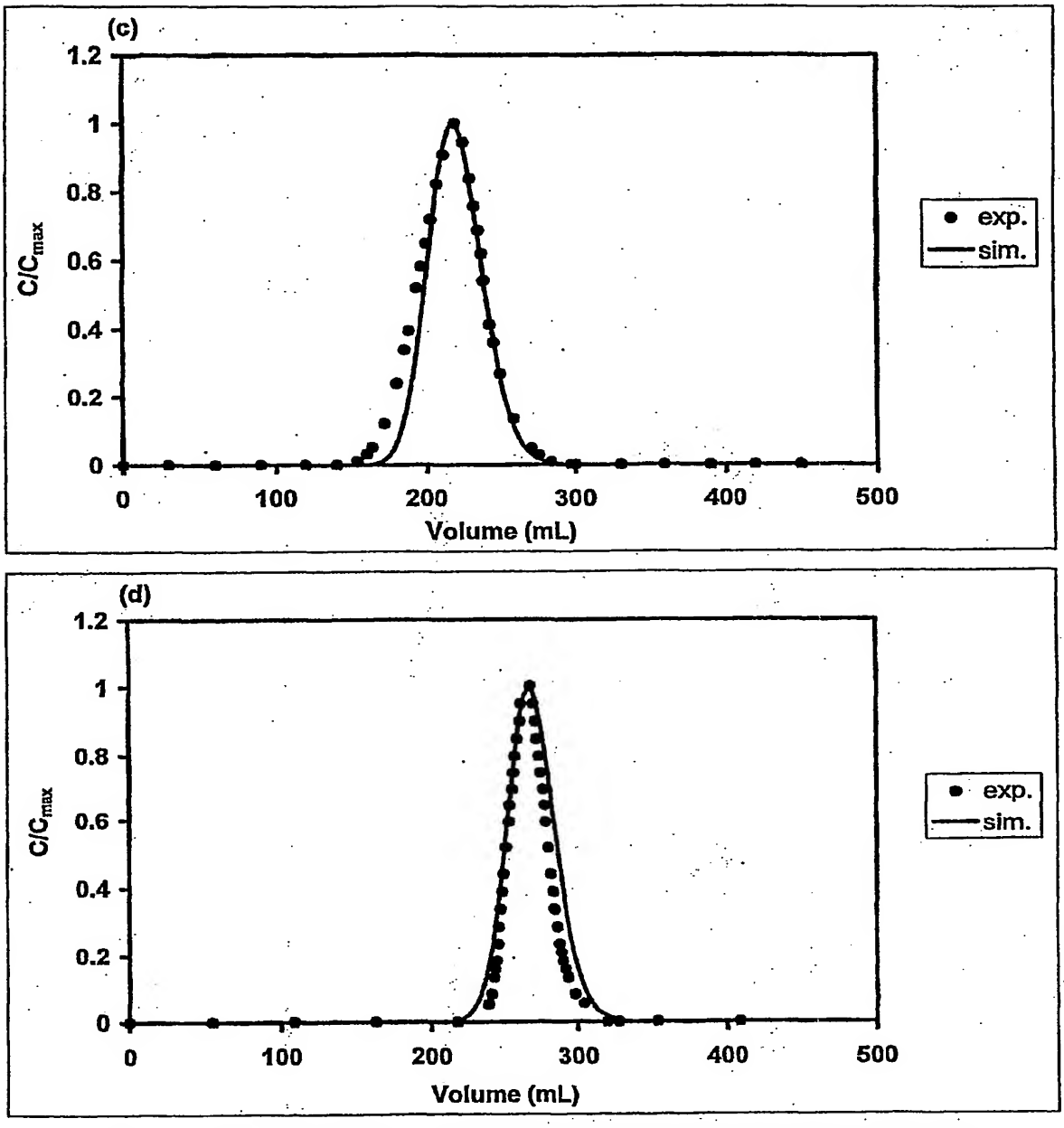

Figure 9 (cont'd). Experimental Data and Simulation Results of the Pulse Tests with a Lab-Scale Column. (c) BHI; (d) $ZnCl_2$.

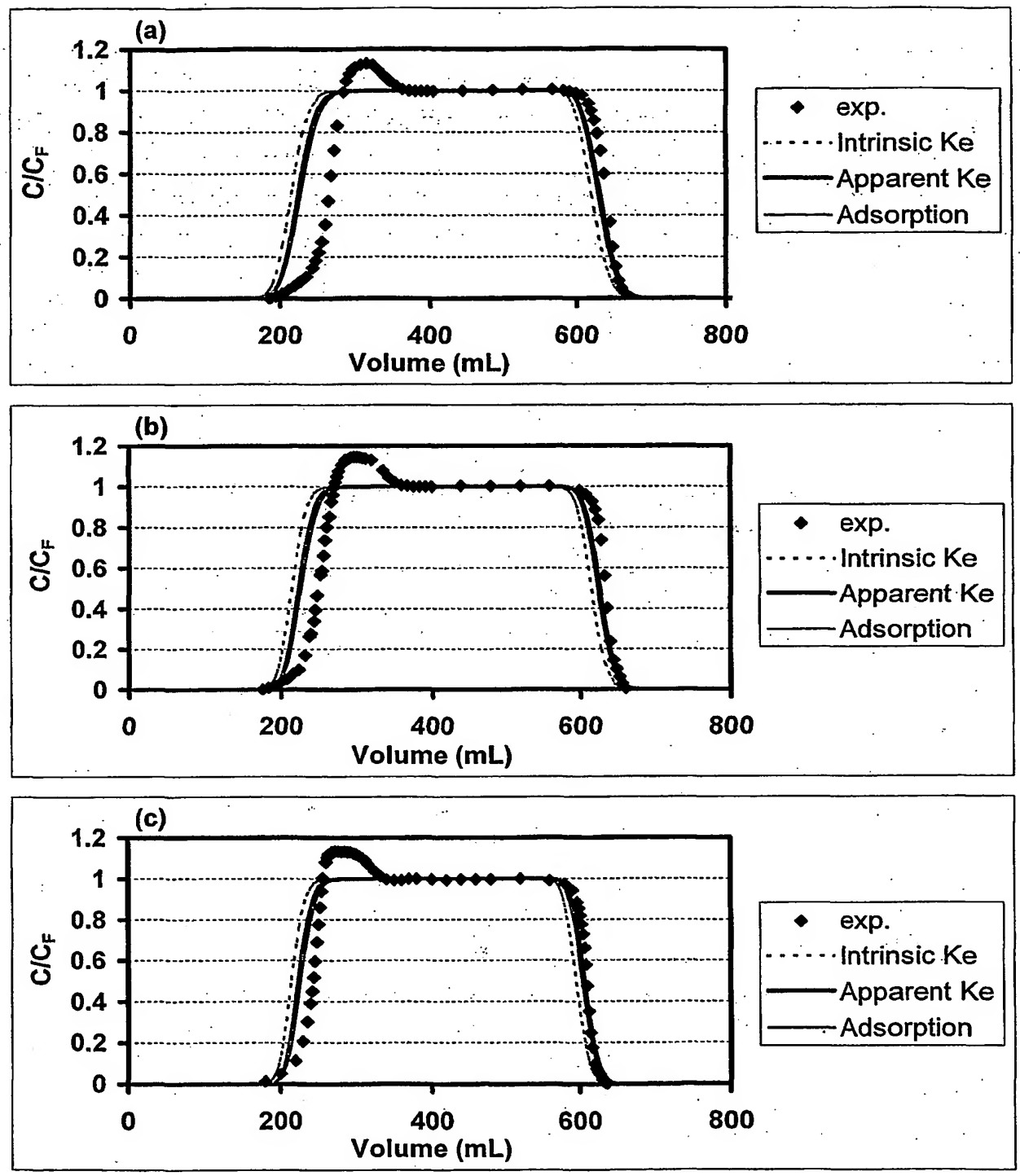

Figure 10. Experimental Data and Simulation Results of the BHI Saturation and Elution Tests with a Lab-Scale Column. Symbols are experimental data and lines are simulations. Flow rate at (a) 8.1 mL/min; (b) 4.0 mL/min; (c) 2.0 mL/min.

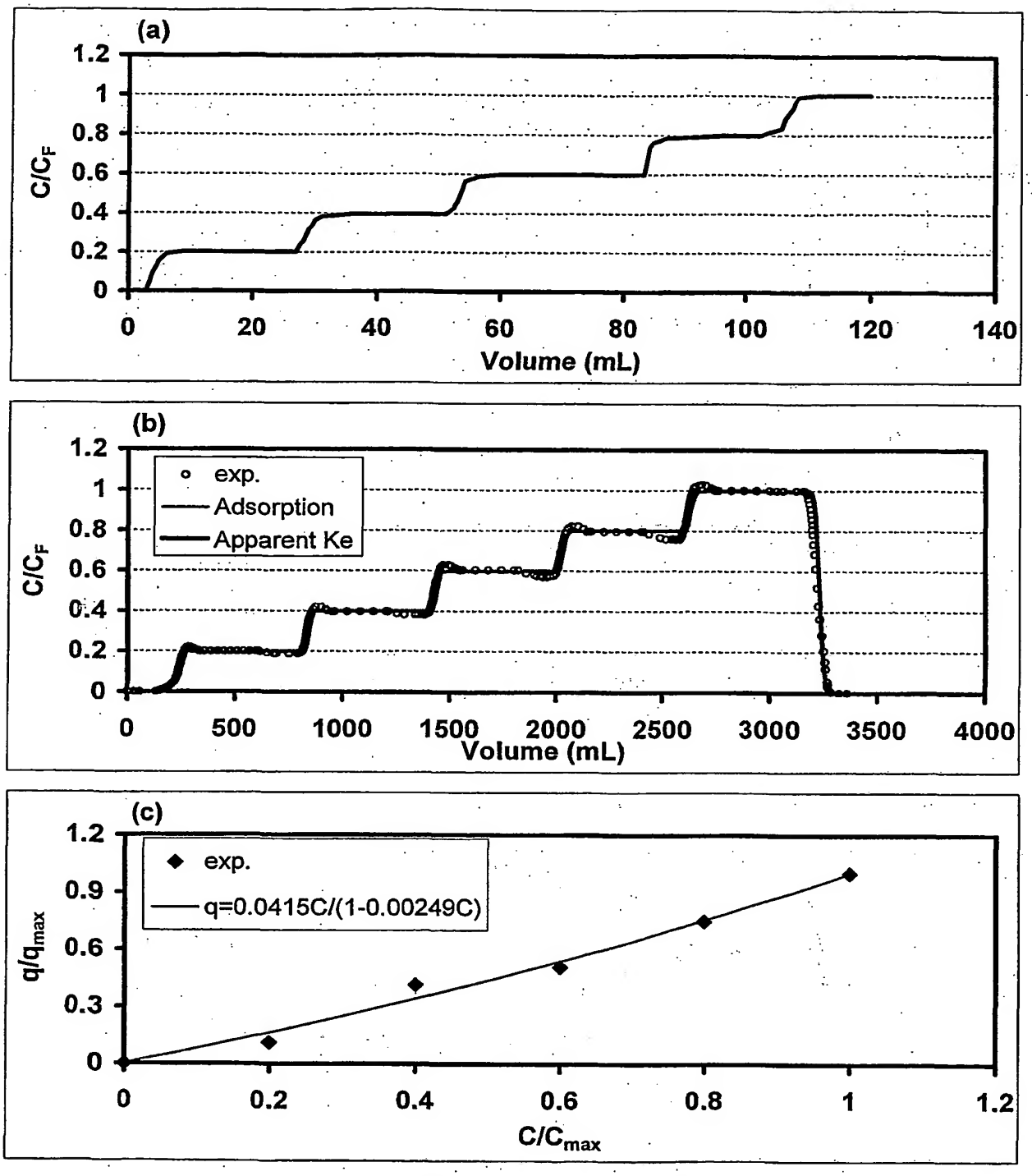

Figure 11. Experimental Data and Simulation Results of the Multiple BHI Frontal Test with a Lab-Scale Column. (a) Multiple frontal data without column; (b) Multiple frontal data and simulation with column. Symbols are experimental data and lines are simulations; (c) Isothermal adsorption data estimated from the multiple frontal tests at 4 °C and fitting with an anti-Langmuir isotherm model.

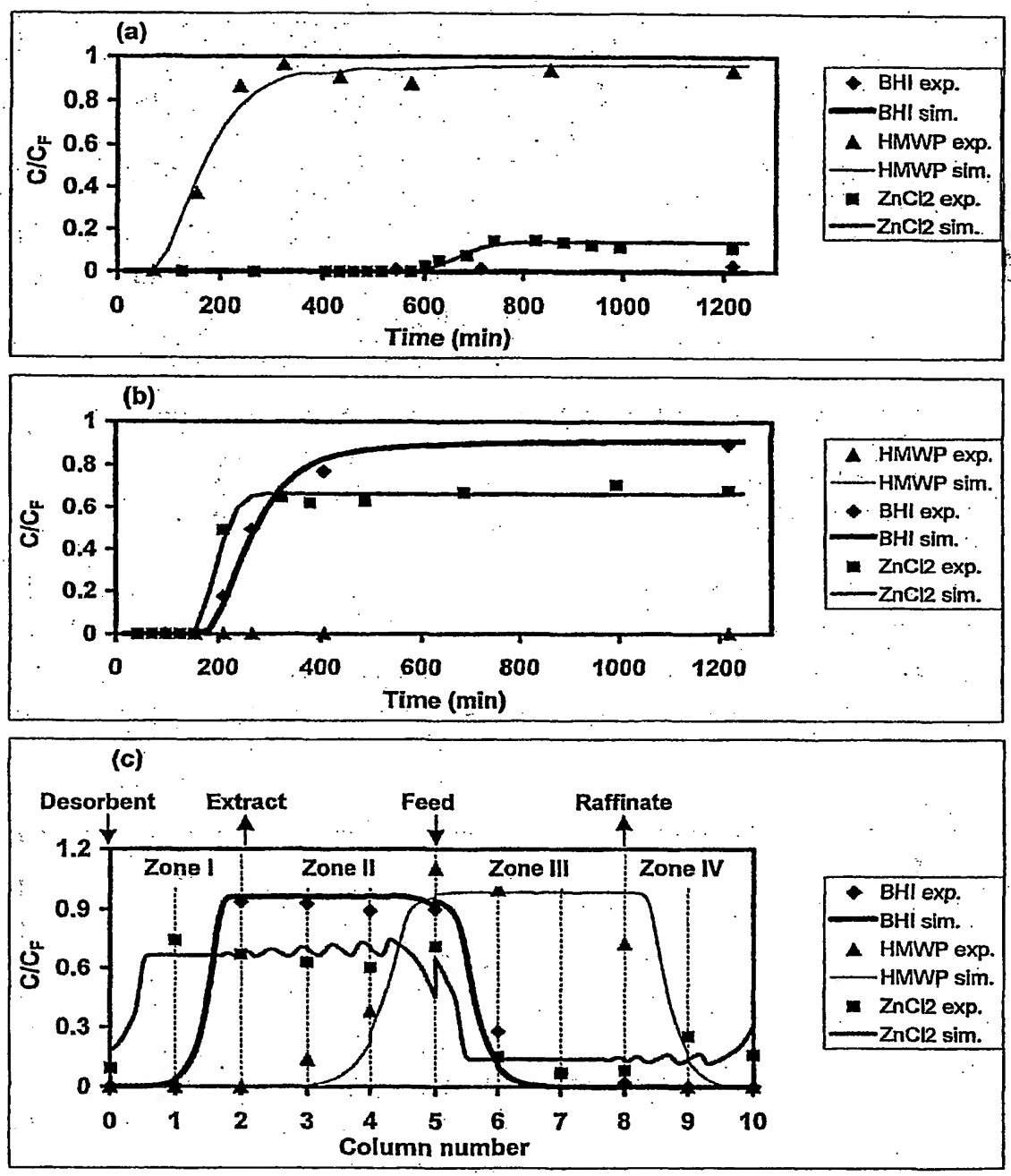

Figure 12 Experimental Data and Simulation Results of the SMB Process Run 1 (Ring I). (a) *Effluent history at the raffinate port*; (b) *Effluent history at the extract port*; (c) *Mid-cycle* column profiles at the 45th cycle. Concentrations in the effluent histories are averaged over one switching period.

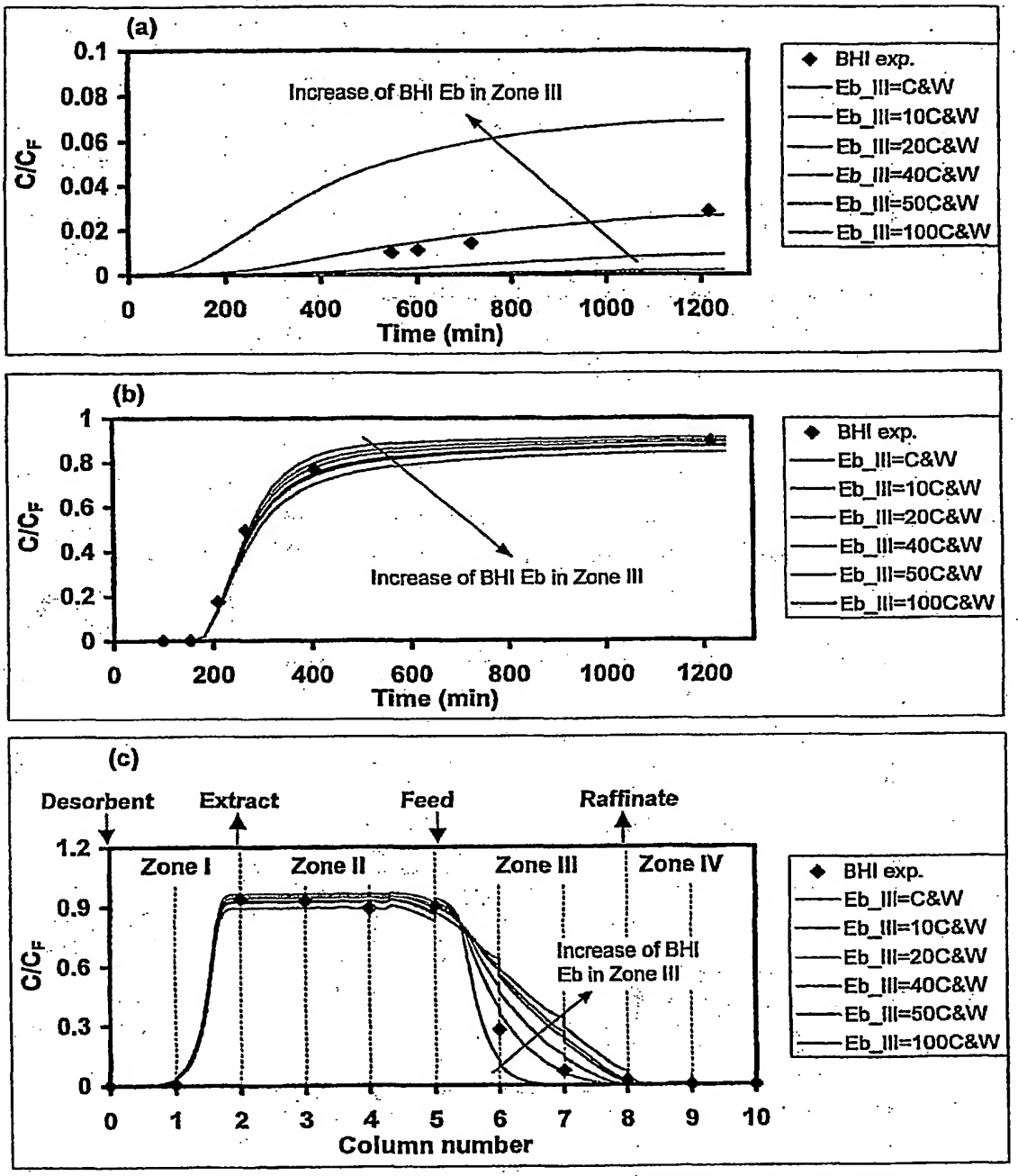

Figure 13 Data of BHI in the SMB Experiment Run 1 (Ring I) and Simulations with Different BHI E_b's in Zone III. (a) Effluent history at the raffinate port; (b) Effluent history at the extract port; (c) Mid-cycle column profiles at the 45th cycle. Concentrations in the effluent histories are averaged over one switching period. C&W stands for the E_b value estimated from the Chung and Wen correlation.

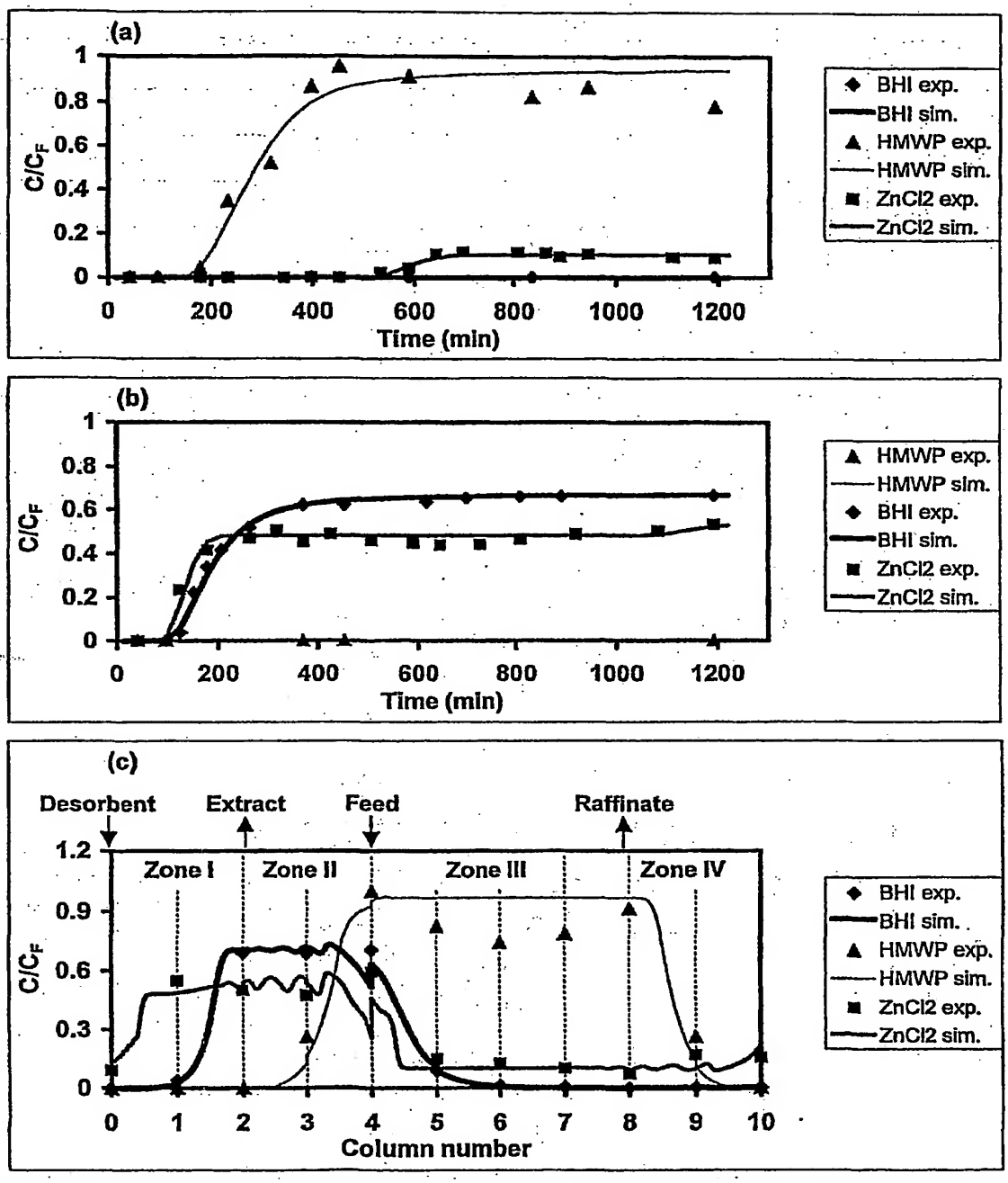

Figure 14 Experimental Data and Simulation Results of the SMB Process Run 2 (Ring I). (a) Effluent history at the raffinate port; (b) Effluent history at the extract port; (c) Mid-cycle column profiles at the 45th cycle. Concentrations in the effluent histories are averaged over one switching period.

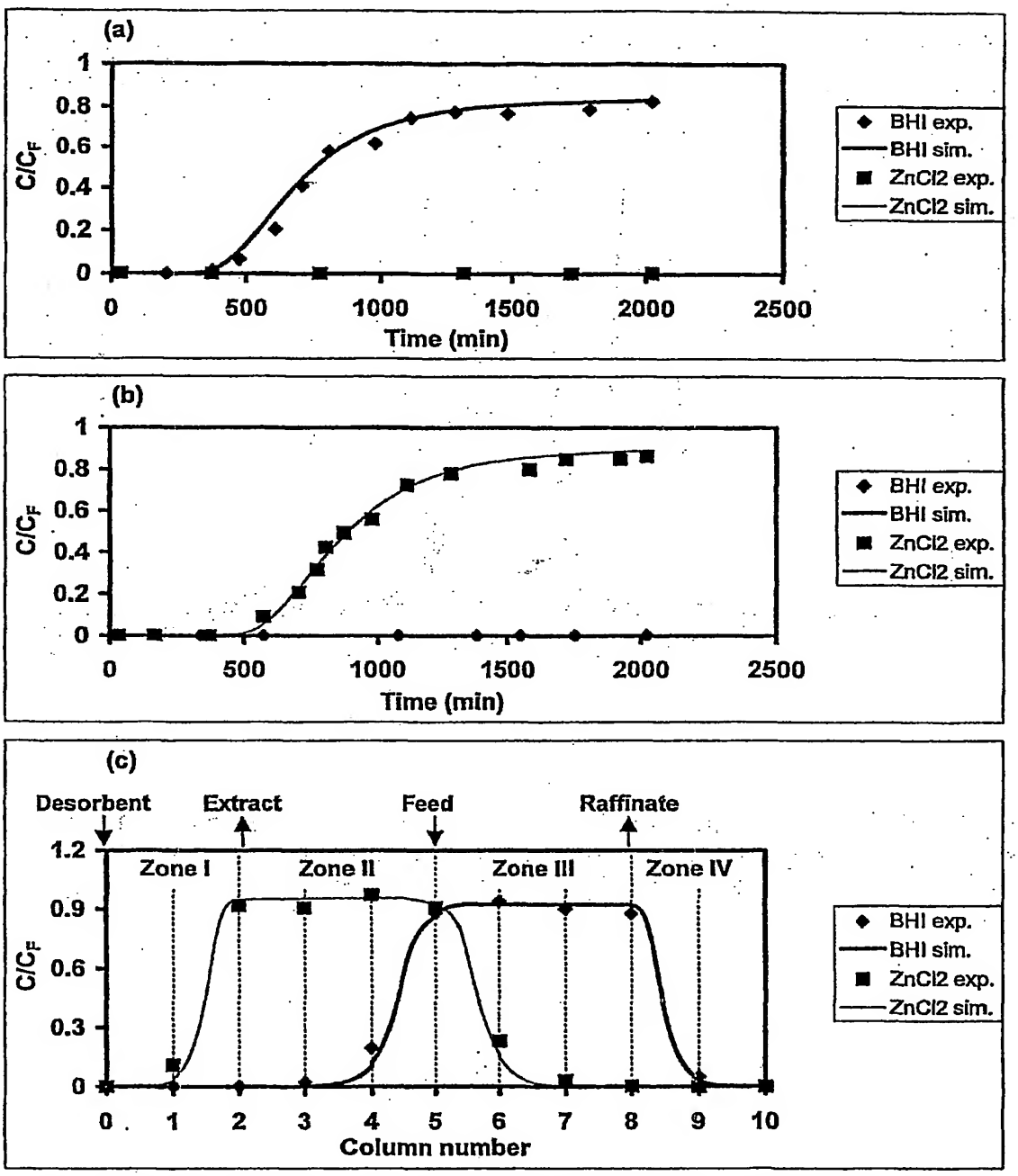

Figure 15 Experimental Data and Simulation Results of the SMB Process Run 3 (Ring II). (a) Effluent history at the raffinate port; (b) Effluent history at the extract port; (c) Mid-cycle column profiles at the 61st step. Concentrations in the effluent histories are averaged over one switching period.

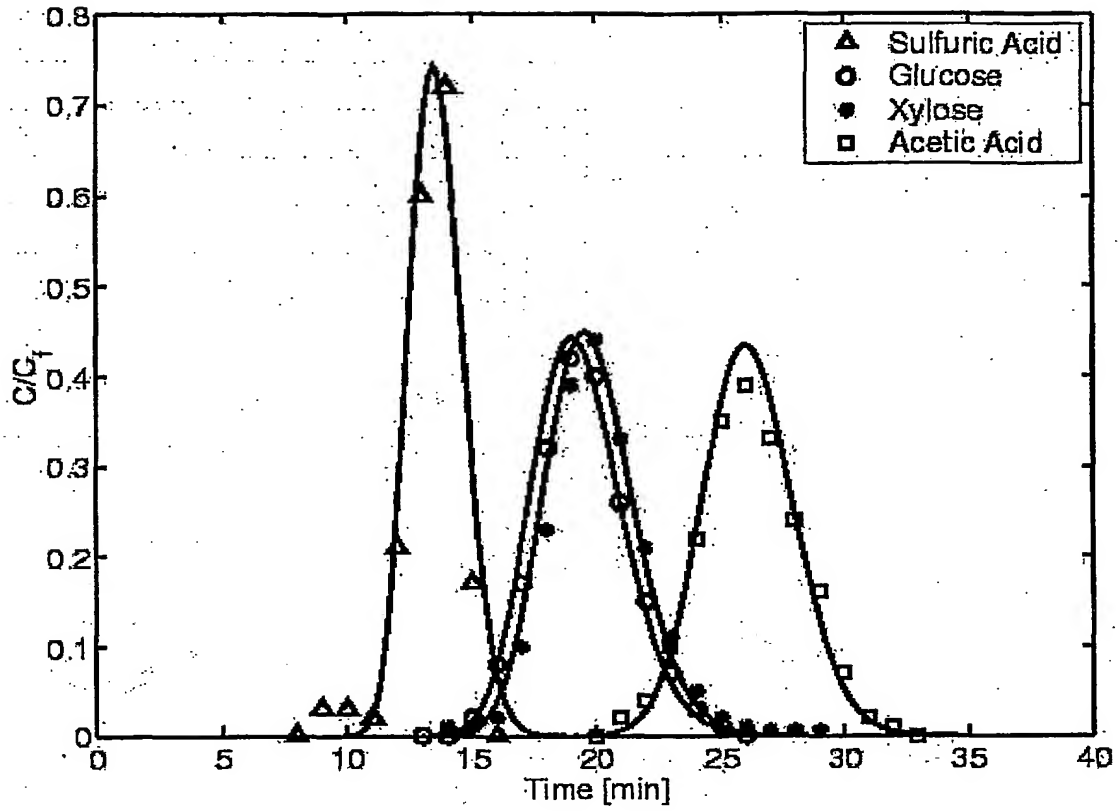

Figure 16. Outlet Concentration Profiles Resulting from Pulse Injections of Sulfuric Acid, Glucose, Xylose, and Acetic Acid at 10 ml/min. $L_c = 55.88$ cm, I.D. $= 2.54$ cm, $V_{inj} = 20$ ml, $\varepsilon_b = 0.35$, $\varepsilon_p = 0.60$, $R_p = 160$ μm. Single-component pulses.

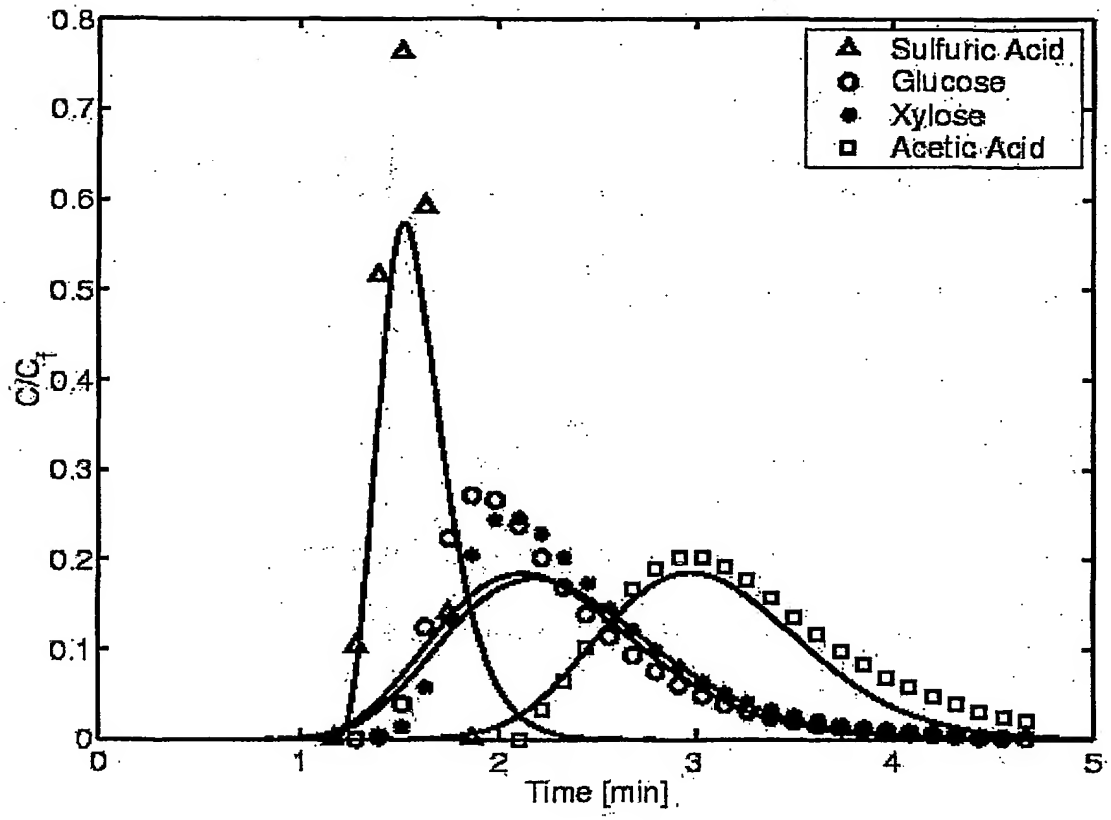

Figure 17. Outlet Concentration Profiles Resulting from Pulse Injections of Sulfuric Acid, Glucose, Xylose, and Acetic Acid at 80 ml/min. Other system parameters are the same as those of Figure 17. Pulse was injected as a four-component mixture.

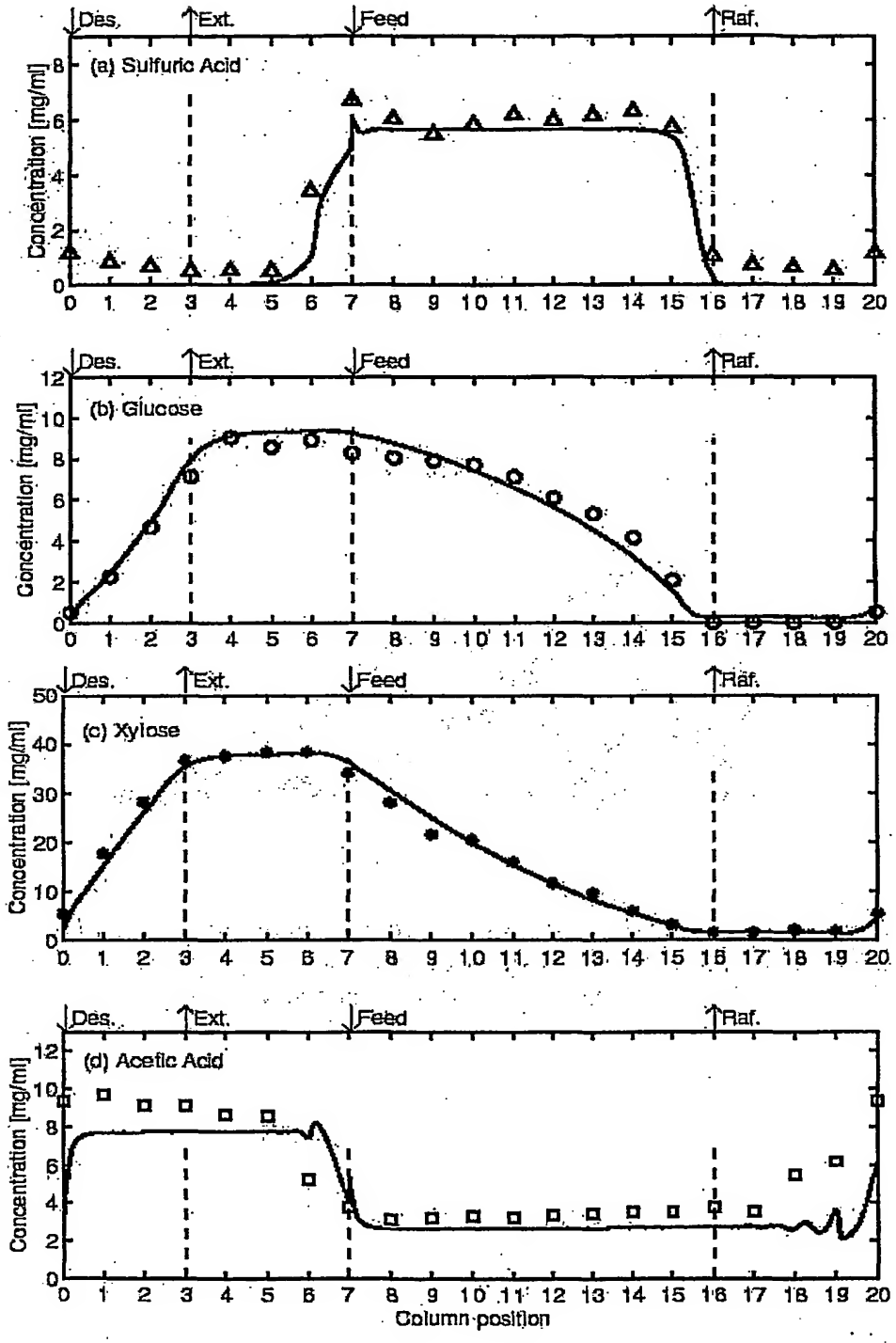

Figure 18. Preliminary SMB Experiment for Removing Sulfuric Acid from Glucose, Xylose, and Acetic Acid. All data are taken from the same SMB experiment. Operating parameters are listed in Table 14. (a) Sulfuric acid; (b) glucose (c) xylose, (d) acetic acid.

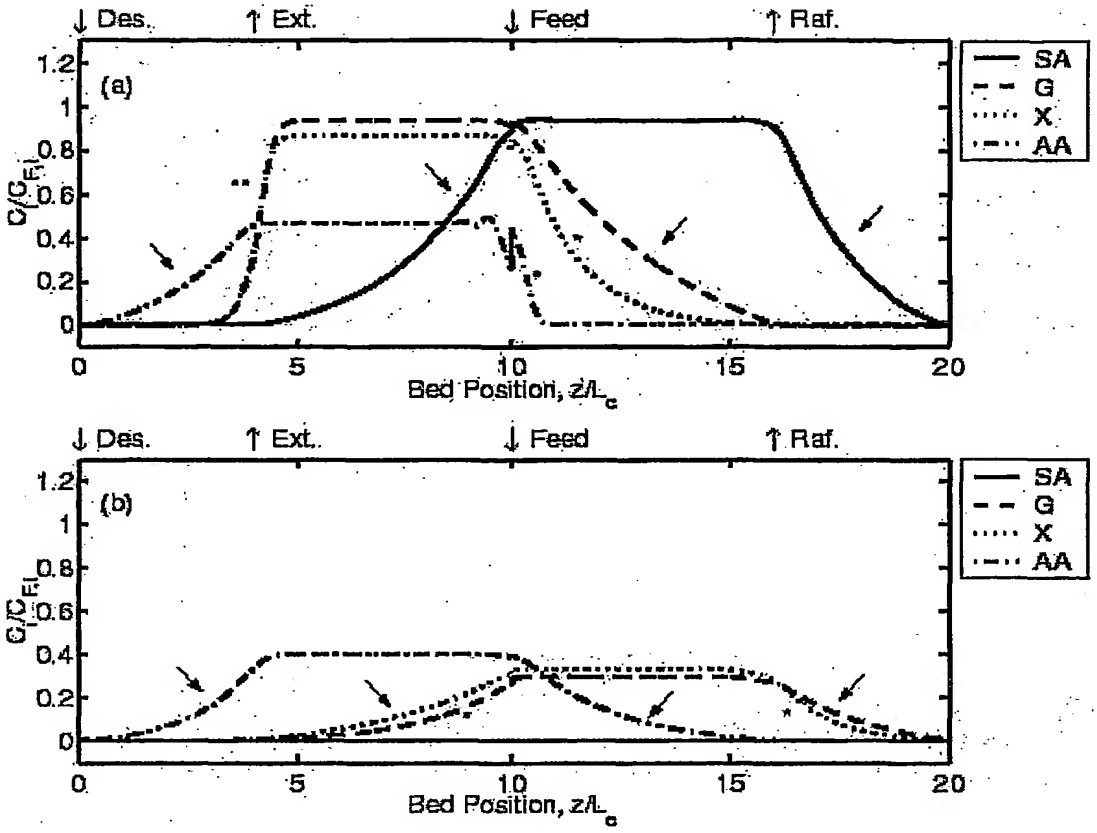

Figure 19. A Tandem SMB Process for Complete Separation; Sulfuric Acid Cleaved First. (a) Complete separation of glucose (G), xylose (X), and acetic acid (AA) from sulfuric acid (SA). (b) Complete separation of glucose and xylose from acetic acid. Arrows (←): standing waves. Asterisks (*): pinched waves.

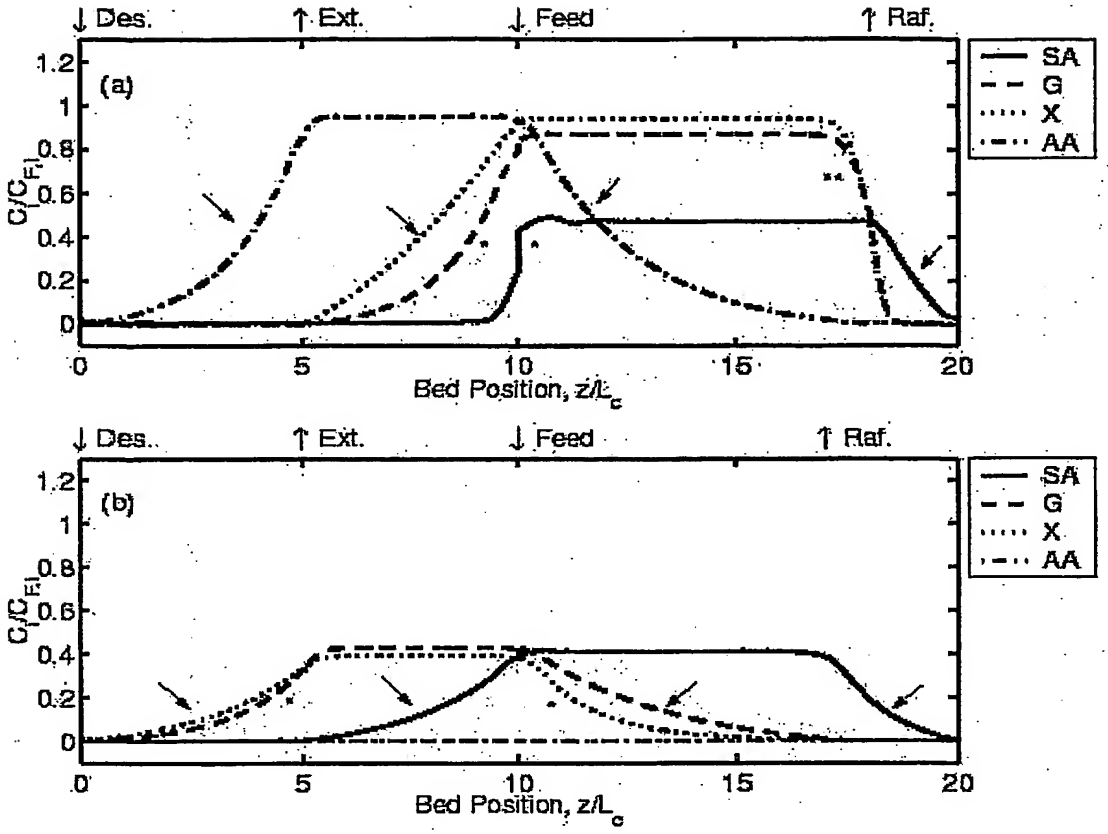

Figure 20. A tandem SMB Process for Complete Separation; Acetic Acid Cleaved First. (a) Complete separation of glucose, xylose and sulfuric acid from acetic acid. (b) Complete separation of glucose and xylose from sulfuric acid.

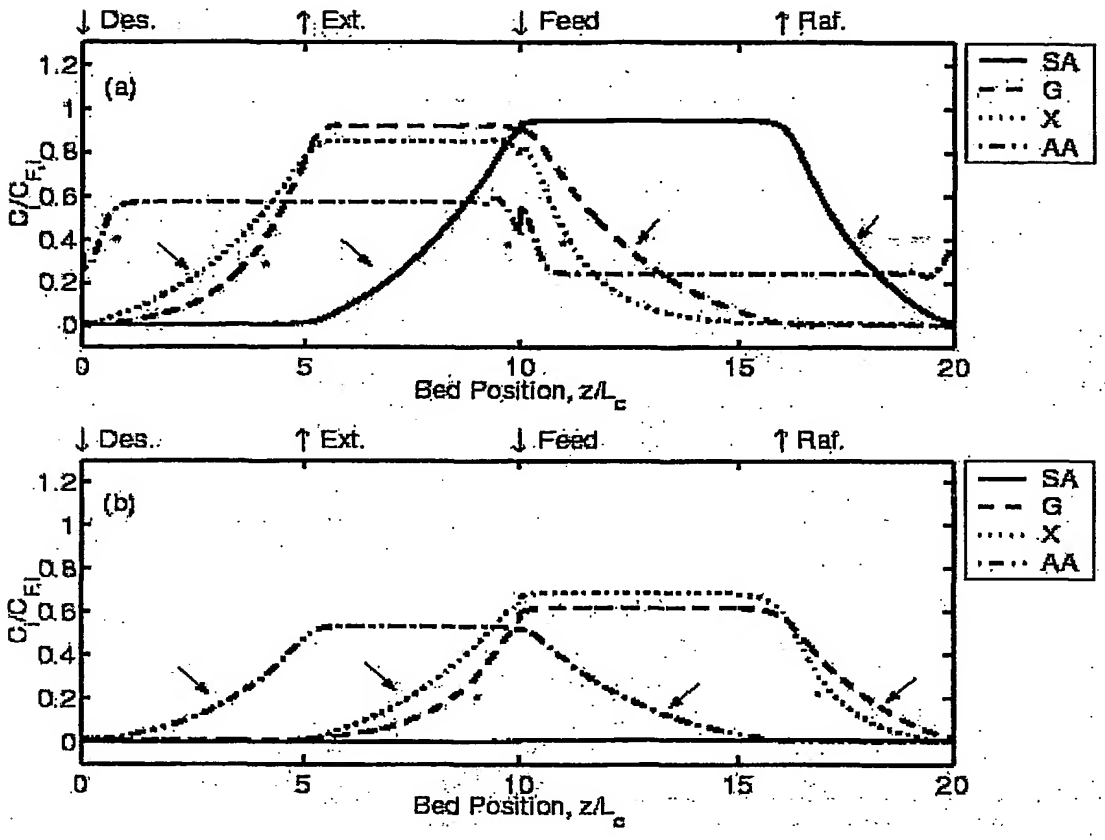

Figure 21. A Tandem SMB Process in which Acetic Acid Distributes between Two Product Ports. (a) Separation of glucose and xylose from sulfuric acid; acetic acid is allowed to distribute between the two product ports. (b) Complete separation of glucose and xylose from acetic acid.

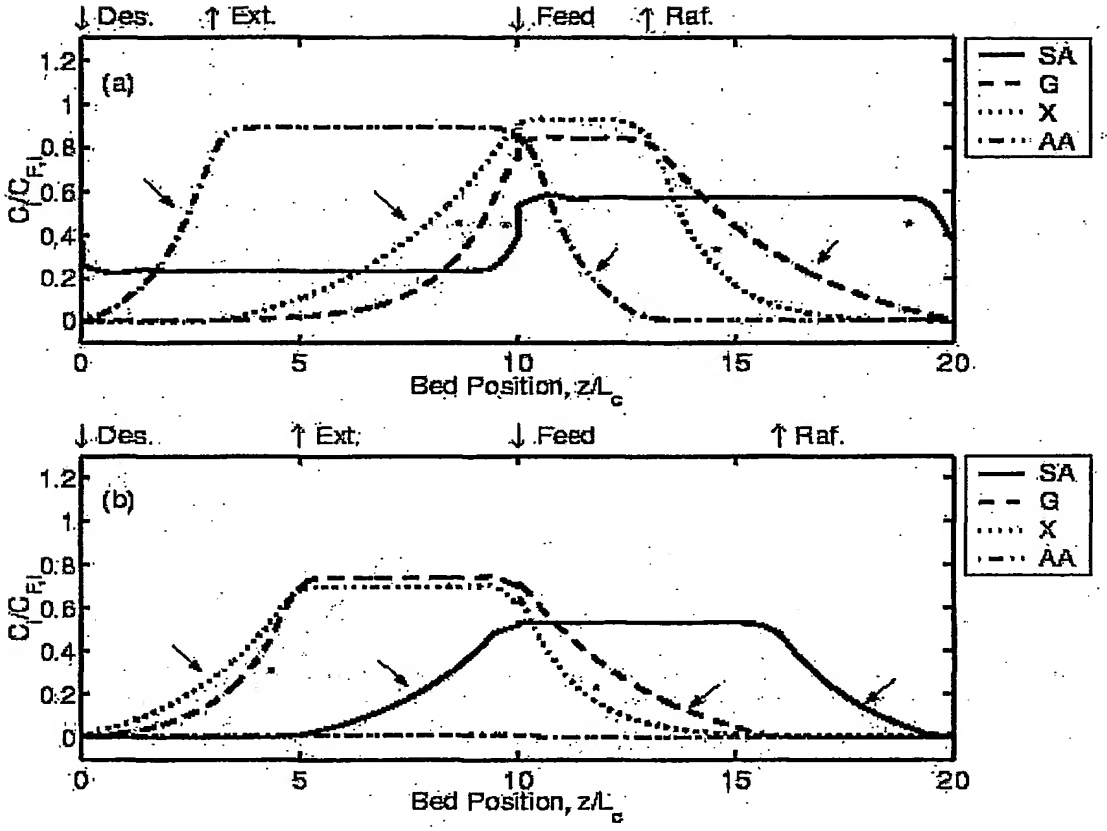

Figure 22. A Tandem SMB Process in which Acetic Acid Distributes between Two Product Ports. (a) Separation of glucose and xylose from acetic acid; sulfuric acid is allowed to distribute between the two product ports. (b) Complete separation of glucose and xylose from sulfuric acid.

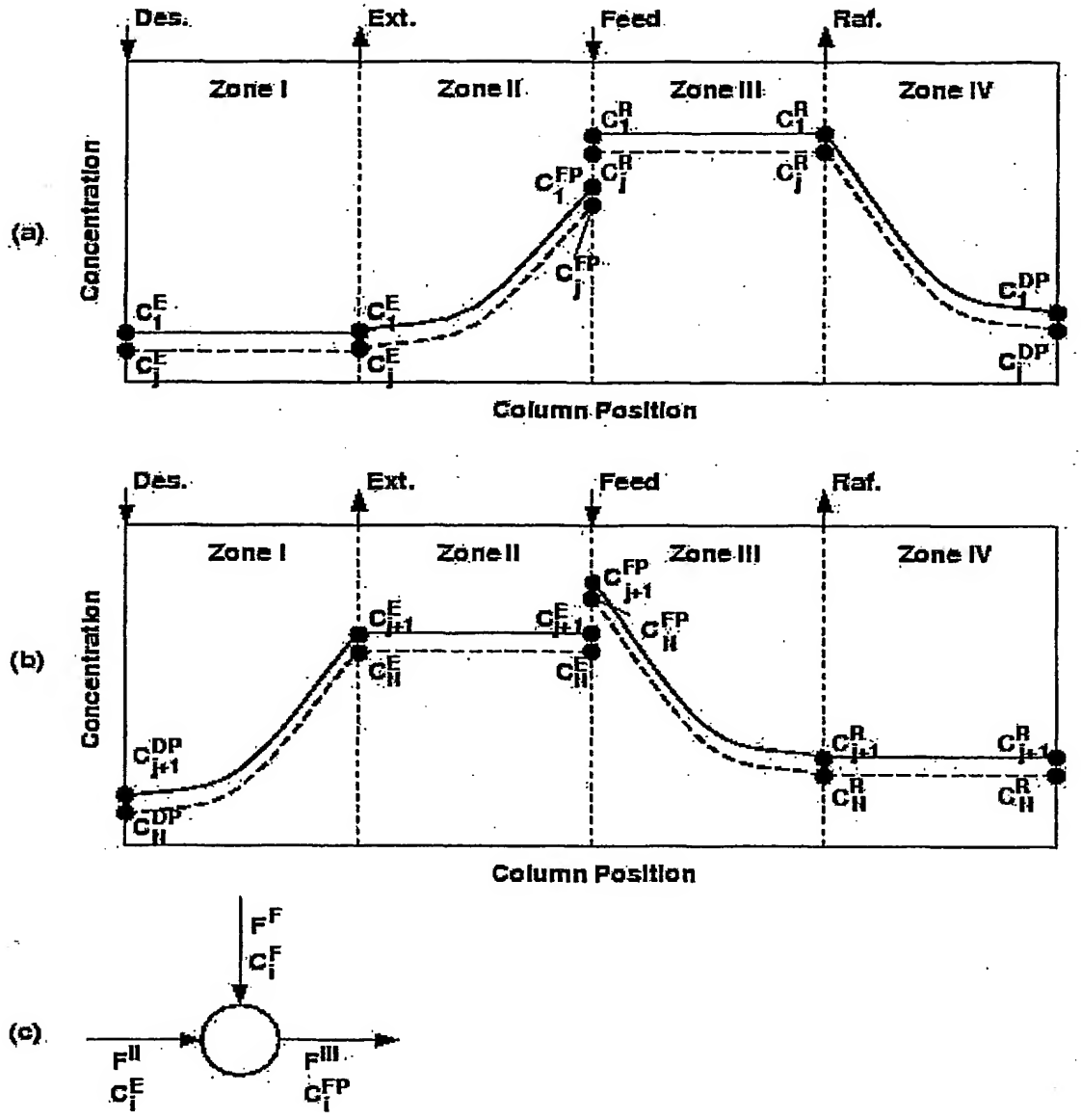

Figure 23. Approximate Column Profiles for the Estimation of Product Concentrations and Decay Factors. (a) Column profiles of typical components to be enriched in the raffinate port ($i \in \{1, \ldots, j\}$); (b) column profiles of typical components to be enriched in the extract port ($i \in \{j+1, \ldots, N\}$); (c) mixing junction at the feed port showing how the mass balance is calculated for a component of the extract.

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WO 01/087452 A3

(54) Title: STANDING WAVE DESIGN OF SINGLE AND TANDEM SIMULATED MOVING BEDS FOR RESOLVING MULTICOMPONENT MIXTURES

(57) Abstract: Separations of one or more components from multi-component fluid mixtures using simulated moving bed technology, and methods of designing such simulated moving beds (SMBs), are provided. The SMBsdesigned according to this invention can be used to separate slow and fast moving fractions in multicomponent mixtures, or to separate an intermediate affinity component from the mixture. The invention is applicable to systems exhibiting linear isotherms, and is especially applicable to such systems when separations are inhibited by mass transfer resistances.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/01/15848

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01D15/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
SCISEARCH, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	XIE Y ET AL: "EXTENDED STANDING WAVE DESIGN METHOD FOR SIMULATED MOVING BED CHROMATOGRAPHY: LINEAR SYSTEMS" INDUSTRIAL & ENGINEERING CHEMISTRY RESEARCH, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 6, 2000, pages 1993-2005, XP001149345 ISSN: 0888-5885	1-5, 10-14, 40,50, 52-54,89
A	page 1996 -page 1998	6-9, 15-39, 41-49, 51,55-88

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Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2003	04/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zinngrebe, U

Form PCT/ISA/210 (second sheet) (July 1992)

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